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THE PATHOLOGY OF TUMOURS

E. H. KETTLE

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THE PATHOLOGY OF TUMOURS

THE PATHOLOGY OF TUMOURS

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PREFACE TO THE SECOND EDITION

THE original plan of this book, to provide a manual for students which should contain the generally accepted teaching on the pathology of tumours without the mass of detail proper in a more ambitious work of reference, has been kept in view in the preparation of the second edition. The text has been revised throughout and much new matter has been added, especially in the sections dealing with Etiology, Experimental Research, the Carcinomata and the Endotheliomata. There are thirty-three new figures, and most of the original photographs of naked eye specimens have been replaced by drawings.

It is a pleasure to acknowledge the kindly criticisms on the first edition ; the suggestions which have been received from many quarters have been carefully considered and, where possible, adopted.

E. H. K.

CARDIFF, 1925.

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PART I

THE GENERAL BIOLOGY OF TUMOURS

DEFINITION

As a result of the enormous amount of labour which has been devoted to the study of new growths since the doctrine of cellular pathology was first enunciated, we have now a fairly clear conception of the nature of true tumour formation. Nevertheless, it is by no means easy to express our ideas in the form of a definition which shall limit successfully their general characters without being unduly cumbersome.

Tumours or neoplasms are composed of collections of new-formed cells derived from, and closely resembling, those found in the normal body, and they therefore bear a likeness to other conditions of cell proliferation such as simple hypertrophies, processes of reaction and repair, and infiltrations. The likeness, however, is only superficial, for tumours are characterised by the possession of autonomy, a property which distinguishes them from all other conditions of cell growth with which we are acquainted.

Autonomy, the term devised by Thoma to express the absolute independence of growth and behaviour distinctive of tumours, is one of the most remarkable phenomena in the whole of pathology. In nearly all other forms of progressive metamorphosis we can assign a cause or attempt an explanation for the formative process, but in the case of the neoplasms we are dealing with a totally different condition. A tumour plays no useful part in the life of the organism as a whole, indeed its influence is often inimical; it performs no helpful function; and its growth is progressive, purposeless, and uncontrolled. Further, we are entirely ignorant of the essential etiological factor.

It is therefore obvious that any definition of tumours must be, in the present state of our knowledge, unsatisfactory and in the nature of a makeshift.

One of the best is that proposed by Powell White : ***"A mass of cells, tissues or organs, resembling those normally present in the body, but arranged atypically, which grow at the expense of the organism without, at the same time, subserving any useful purpose therein."***

Although there are rare cases in which tumours do not fulfil the conditions thus laid down, the definition, on the whole, expresses satisfactorily all the features we are entitled to claim for them. And it has the added advantage of omitting any reference to causation.

Theoretically, then, we should be able to decide, from a study of its structure and mode of growth, whether any formative process is a true neoplasm or whether it is to be regarded as one or other of the various conditions we have mentioned. In practice, however, the distinction may be extremely difficult to determine ; and there are borderland cases in which it is impossible to make any decision.

STRUCTURE

Structure of Tumours.—All tumours are derived from pre-existing cells of the body and resemble them more or less closely. In some cases the resemblance is so marked that the source of origin is never for a moment in doubt ; on the other hand, the histology of the growth may differ so widely from the normal that it is only after careful study of a series of such growths that we are able to decide on the parent tissue. The former class are known as ***typical***, and the latter as ***atypical.***

Tumours consist of two parts, a connective tissue matrix or stroma, and the parenchyma or tumour cells proper : it is the latter portion which gives the tumour its distinctive character. The relationship between stroma and parenchyma varies very considerably in different growths, or even in different portions of the same growth. In those of the epithelial or glandular type the two constituents are easily distinguishable, and the stroma may be more abundant than the parenchymatous element ; but in the connective tissue group the reverse holds good, and it may be quite difficult to demonstrate any matrix whatever.

Parenchyma.—Speaking generally, the innocent growths are typical, and the parenchyma cells bear a strong likeness to the normal cells of the tissue from which the tumour arose. So close is this likeness that it is only by a study of the arrangement of the cells that we are able to distinguish the neoplastic nature of the condition. In malignant tumours, on the other hand, the cells differ considerably from their normal prototypes; that is to say, malignant growths are atypical, and their cells tend to assume the embryonic or immature form so that it may be difficult, if not impossible, to determine their origin. Not only are the individual cells atypical, but their arrangement or relationship to one another varies widely from the normal; and they are peculiarily liable to degenerative processes.

Between these extremes all grades may exist, giving rise to the various types of tumour which we have to study.

Similar differences are seen in the physiology of tumours and may be reflected in their histology. Those of the innocent type often retain some of the functions of the tissues from which they originated. Thus, an adenoma of mucus secreting epithelium tends to produce mucus, though the production is imperfect or perverted; tumours of the thyroid gland commonly contain colloid; liver tumours may form bile; while in growths of osteogenetic tissue the formation of true bone may occur. In malignant tumours such behaviour is, at the best, imperfect, and is usually absent. Many carcinomata of the rectum produce little or no mucus; an osteosarcoma contains osteoid tissue rather than true bone, and so forth.

In this connection, Beckton's [1] work on Altmann's granules is of importance. The exact significance of these granules, and the part they play in the physiological activities of the cell, are uncertain, but, by a modification of Altmann's original technique, Beckton has shown that they may be demonstrated in nearly all varieties of normal cells. They are, however, absent in practically all malignant growths of the human subject, and it is suggested that we have, in the presence or absence of granules, a valuable sign in the diagnosis of malignancy. But it must be pointed out that Altmann's granules are probably simply part of the mitochondrial system of the cells, to which a good deal of attention has been devoted in recent years; by more elaborate methods they may be demonstrated in all cells, innocent and

[1] *British Medical Journal*, 1909.

malignant, so that the test cannot be considered an absolutely clean one.

Very important changes occur in the nuclei of the parenchyma cells. In the typical growths the nuclei are more or less normal, but the atypical forms may present profound variations: these consist of alteration in size and shape, multiplications, degenerations, and pathological forms of division. In the older parts of the tumour the nuclei may be shrunken and distorted, deficient in chromatin (chromatolysis), or fragmented (karyorrhexis). At the growing margin the nuclei may show great variations in size, both from the normal and from each other, while cells containing two or more nuclei may be encountered, and, indeed, are characteristic of certain forms of tumour.

Irregularities in mitoses are common. There may be a diminished number of chromosomes (hypochromatic mitosis), or an increased number (hyperchromatic mitosis); the mitosis may be asymmetrical, and, resulting from an excess of centrosomes, we may encounter pluripolar forms.

Stroma.—The stroma of a tumour is derived from the connective tissues of the organ in which it is growing, and is of the nature of a reaction against the tumour cells. When carried to extremes, the reaction may be so excessive as to choke the neoplastic elements and give rise to real or practical cure. But in the vast majority of cases it is merely sufficient to support the parenchyma cells and provide them with nourishment. Here we may note that this stroma reaction is vital to the life of the neoplasm; if the tissues of the host do not react, providing a framework with nutrient vessels for the parenchyma, the tumour is unable to live.

It is in the innocent group that the essential nature of the stroma is most obvious, for here stroma and parenchyma grow side by side, the one increasing with the other. In the malignant growth, on the other hand, the parenchyma invades and absorbs surrounding tissues, thus constantly adding to its stroma by this means as well as by a fresh formation.

In some tumours the parenchyma has a powerful influence in determining the nature of the stroma. Thus, the framework may be extremely meagre in amount, consisting chiefly of capillary blood vessels with an occasional delicate meshwork of collaginous fibrils; or it may be abundant and composed of dense fibrous tissue; or it may undergo various changes such as

calcareous degeneration; or it may even be stimulated to undergo a neoplastic change itself.

It is obvious that, in order to live, a new growth must receive nourishment and must also be provided with drainage in the form of lymphatics to remove its metabolic products. These are supplied by the stroma.

In innocent tumours the blood vessels are, as a rule, fairly well developed, but in the malignant group they are always undifferentiated, consisting for the most part of capillaries or sinuses, and often lying in direct continuity with the tumour cells; while the lymphatics consist simply of lymph spaces.

Occasionally one may encounter formed vessels in the substance of a malignant growth; but these are the vessels of the tissue which has been invaded, and they constantly exhibit a varying amount of endarteritis.

Tumours themselves are devoid of sensation, and, as we should expect, no nerves are present in them. A malignant growth may envelop the nerves of the tissue it is invading, but these are limited to the periphery, and none are present in the substance of the growth.

GROWTH

It is generally held that tumours arise from one cell or group of cells, and not as the result of a change affecting a comparatively large area. Whatever may be the size of the tumour, all its cells are the direct descendants of the mother cell or cells.

While this is the accepted teaching of a large school of pathologists, some authorities maintain that cells in the neighbourhood of a new growth may be stimulated to undergo abnormal proliferation, resulting in the production of an independent tumour; this subsidiary growth fuses with the primary one and, therefore, multiple foci of origin may occur. Often enough the epithelial cells adjacent to small carcinomata of the tongue or intestine show obvious histological departures from the normal, but it is of course impossible to prove that this change is preliminary to definite malignant transformation. By the study of serial sections of certain small malignant growths it can sometimes be demonstrated that what appears to the naked eye to be a single tumour really consists of two or more separate growths in close juxtaposition. Even if this be accepted, it merely means that

an organ or area of the body is the site of multiple tumours, not that a neoplastic process has extended from a tumour to surrounding healthy tissues. In spite of anomalous appearances, and of occasional phenomena encountered in the experimental study of cancer, tumours must be regarded as being of unicentric, and not multicentric, origin.

From our definition we see that the growth of a tumour is progressive and uncontrolled. The rate of growth varies very considerably in different types, and even in the same example from one interval of time to another. For the most part the typical tumours grow slowly and the atypical forms rapidly. Both varieties, but especially the atypical, are subject to sudden exacerbations, and, as has been demonstrated in the studies of the Imperial Cancer Research Fund, propagable malignant tumours show a constant cycle of waxing and waning growth.

The mode of growth is of importance, and differs in the two main varieties. In the typical forms the increase of substance is uniform, or tends to be so, throughout the whole mass ; but in the atypical forms peripheral extension is the rule, with little or no growth in the central parts. In other words, the increase of size is by ***expansion*** in the one form and by ***infiltration*** in the other, and, as we shall see, this difference plays a dominating part in the life history of the growth.

The growth of a tumour is independent of the physical condition of the host. However emaciated the host may be, the tumour itself is well nourished and makes the first claim upon such resources as remain to be drawn upon. This is well seen in experimental animals fed on a diet deficient in tryptophane, a substance which is essential for life and must be supplied in the food, since it cannot be synthetised in the body. In such animals Cramer [1] has shown that transplanted tumours grow as readily as in the normal controls, but the onset of the fatal symptoms of this deficiency disease is definitely hastened by the presence of the growing tumour. In other words, the tumour demands and receives from its host such small quantities of tryptophane as may be available, though the life of the animal is sacrificed thereby.

On the assumption that they are necessary for growth, it has been suggested that the absence of ***vitamins*** from the diet might influence adversely the growth of tumours, and the treatment

[1] *Eighth Scientific Report, Imperial Cancer Research Fund*, p. 17.

of cancer has actually been attempted along these lines. It has been shown experimentally, however, that the rate of growth of tumours in animals fed on a vitamin-free diet does not differ materially from that seen in control animals on a normal diet; nor does an excess of vitamins exercise any influence on the neoplasms. Apart from the important bearing these observations have upon the general action of vitamins, they demonstrate that dietetic restrictions of this kind have no value in the treatment of malignant disease.

INNOCENCY AND MALIGNANCY

As a matter of practice it is usual to divide all tumours into two main classes, the innocent and the malignant, according to whether or not they exhibit certain features in the course of their growth.

Although this division is a theoretical possibility, as a matter of fact it is often extremely difficult to assign a particular growth to its proper class.

In the first place, we have to distinguish between clinical and pathological malignancy. Clinically, any tumour which causes the death of the host is a malignant one, that is to say, the effect on the host is the criterion of the type of the tumour. Pathologically, a malignant tumour is one which possesses certain properties, and although we know from experience that such a growth is almost invariably fatal, it is in respect to these properties and not to the ultimate fate of the host that we assign to it a place in the malignant group. Thus, an annular carcinoma of the rectum, an innocent tumour of the uterus or ovary, or a sclerosing inflammatory process may all cause intestinal obstruction and death, though in the first instance only is the fatal result due to a malignant growth.

This distinction between clinical and pathological malignancy is of the very greatest importance from the point of view of the statistical investigator into the nature of cancer, and failure to recognise it has rendered many statistics useless. For instance, as Bashford has pointed out,[1] all fatal diseases of the prostate gland are, in Switzerland, included under the heading of cancer. Young[2] states that 10 per cent of the

[1] *Third Scientific Report, Imperial Cancer Research Fund.*

[2] *Johns Hopkins Hospital Report*, 1906.

enlargements of the prostate are malignant in nature, and this estimate appears to me to err on the side of generosity; but even so, it is obvious that the majority of untreated enlargements of the prostate giving rise to fatal results are clinically and not pathologically malignant.

The accepted signs of malignancy are the following:

(*a*) Rapidity of growth.
(*b*) Vegetative or embryonic character of cell.
(*c*) Infiltration.
(*d*) Formation of metastases and local recurrence after removal.
(*e*) Ulceration.
(*f*) Tendency to central degenerative changes.
(*g*) The occurrence of cachexia and anæmia.
(*h*) Power of continuous growth.

As I shall show, many of these signs may be, and frequently are, absent, and even when present may be highly misleading, but a careful consideration of them will usually enable us to determine the nature of any particular tumour.

(*a*) **Rapidity of Growth.**—This when present is an indication of malignancy, but the reverse does not hold; a slow-growing tumour is not necessarily innocent. Since a malignant tumour is, as a rule, painless in its earlier stages, and may give rise to no symptoms, it is impossible to guess at the duration of the majority of internal growths with any approach to accuracy. But there is little doubt that many of them are of comparatively slow growth, and this is certainly true of numbers of external ones. A rodent ulcer grows slowly, and the same may be said of other forms of carcinomata arising from the skin, yet they are undoubtedly malignant.

Microscopically, rapidity of growth is shown by evidence of cell division and compression of neighbouring structures. It is generally accepted that numerous mitoses indicate a fairly rapid growth and, therefore, a high degree of malignancy, while compression and displacement of surrounding tissues are obvious evidence of rapid increase in the size of the tumour.

(*b*) **Vegetative or Embryonic Character of the Cells.**—It was pointed out by v. Hansemann many years ago that the cells of tumours tend to revert to the primitive or embryonic type. To this reversion he gave the name of anaplasia, and he demonstrated that it is more marked in the malignant than the innocent growths, often being extreme in the former group.

PLATE I

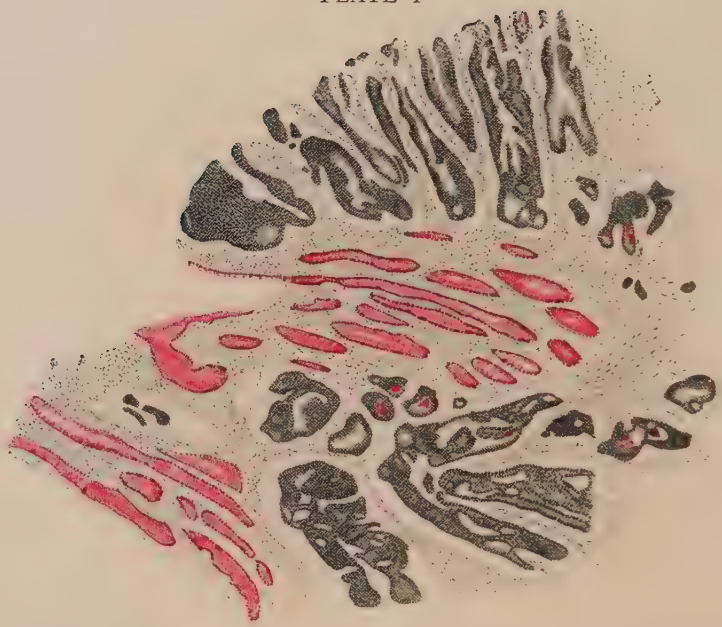

FIG. 1.—Rapidly growing carcinoma of rectum, stained with hæmatoxylin and muci-carmine. The normal epithelium to the left of the figure takes the carmine stain, but very little mucin is formed by the malignant cells.

Zeiss obj. aa. Comp. oc. 4. Tube length, 160 mm.

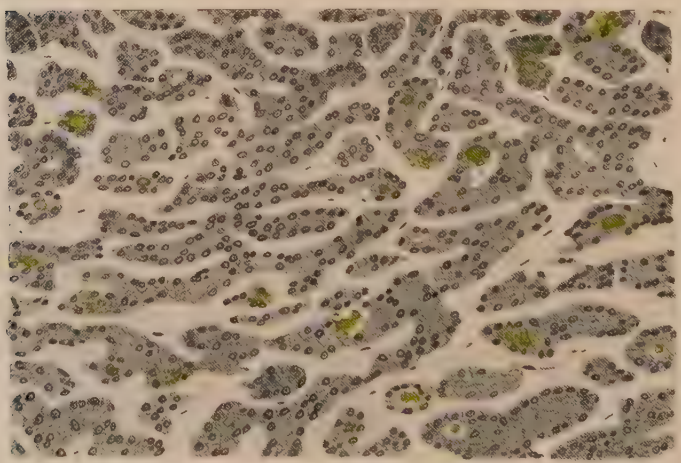

FIG. 2.—Slowly growing liver-cell carcinoma stained with hæmatoxylin. In their form and arrangement the malignant cells closely resemble the normal, and there is a plentiful secretion of bile (stained green).

Obj. 8 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

To face p. 9

A cell has two main functions, those of growth and work, and in the more malignant tumours we find the former character highly developed at the expense of the latter. One of the main functions of the mucous membrane of the large intestine is the production of mucus, and in the innocent, or relatively innocent, tumours of the large intestine we constantly find the cells of the growth secreting mucus. In the more malignant tumours of this region, however, the cells change in type; the cytoplasm diminishes in amount, the nuclei are relatively larger than normal, goblet cells are absent, acini are irregularly formed, and there is little or no attempt at the production of mucus (Fig. 1). In certain very highly malignant types of rectal carcinomata there is, it is true, an extreme mucoid degeneration resulting in the "colloid" cancer, in which the majority of the parenchyma cells are destroyed and replaced by mucus; but this process is a degeneration and in no way to be compared with a physiological function.

In carcinomata of the thyroid, both in the primary tumour and in the metastatic deposits, the growth in certain instances appears to produce colloid, and carcinomata of the liver, especially the more innocent forms, produce bile (Fig. 2); but in spite of these and other examples we find that, as a general rule, the cells of malignant tumours lose their physiological function and devote themselves entirely to growth.

A variable degree of anaplasia, then, is the rule in malignancy, but too much reliance must not be placed upon it as a diagnostic sign. It cannot be too strongly emphasised that it is impossible to recognise an isolated cancer cell as such; it is only by a consideration of the histological structure of the tumour as a whole that we are able to arrive at a diagnosis.

(*c*) **Infiltration**.—As has been pointed out in the section on growth, an innocent tumour increases in mass uniformly throughout its substance, compressing the surrounding tissues to form a pseudocapsule. There is a certain amount of reaction on the part of the tissue adjacent to the growth, resulting in the formation of a loose zone of areolar inflammatory tissue which is easily torn through, making the apparent encapsulation more obvious, and permitting of the familiar process of "shelling out." In malignant tumours, on the other hand, the growth is mainly peripheral, and there is little compression or pushing aside of the adjacent tissues; but there is an active invasion on the part

of the peripheral cells of the tumour, which insinuate themselves between muscle fibres, into tissue spaces, lymphatics, and blood vessels. This infiltrative growth is by no means always obvious to the naked eye, and a small malignant tumour growing in loose areolar tissue, or a yielding organ such as the lung, may appear to be encapsuled. Thus, in the experimental study of cancer where propagation is secured by the inoculation of small fragments of tumour into the loose areolar tissue under the skin, the resulting tumour is commonly of rounded form and apparently not adherent to skin or body wall; yet eventually it becomes fixed, and metastases develop. In other words, as long as a tumour has room to grow and expand it will do so without the destruction of tissue; only when confined and compressed does it exert its infiltrative properties. From anatomical considerations, however, it is obvious that a human malignant growth can only maintain its footing by the destruction of healthy tissue, and accordingly we always find infiltration in progress at the margin of any considerable growth. Microscopically, infiltration is perhaps the most important sign in the diagnosis of malignancy. When present, it enables us to diagnose the condition from the examination of a single preparation without any further knowledge of the case.

(*d*) **Formation of Metastases and Local Recurrence after Removal**.—Although there have been recorded instances of otherwise innocent tumours which have formed metastases, these cases are so excessively rare that the production of a metastatic tumour must be considered an unequivocal sign of malignancy.

By the term metastasis we mean the formation at a distance from the original tumour of a secondary tumour having similar characteristics to the primary one, and obviously derived from it. The question of secondary growths is one of very great importance and will be dealt with in detail later; it is sufficient for the present to note that they occur eventually in the life of practically every malignant tumour, that they vary in size and number within very wide limits, and that they may appear early or late in the course of the disease. From what I have said in the preceding section with regard to encapsulation and infiltration, it is clear that the boundaries of a malignant tumour are widespread and ill-defined, and this is the explanation of the fact that such growths are peculiarly liable to recur after removal. It is common knowledge that a wide margin of healthy tissue

must be included in the removal of any malignant tumour if there is to be any hope of a permanent cure, whereas an innocent growth may be "shelled out" of its capsule with no anxiety as to its recurrence. However, there are numerous exceptions to this rule. Malignant growths are constantly removed with perfect success; were it not so, the disease would be even more terrifying than it is; and, contrariwise, local recurrence may, and does, occur after the removal of a perfectly innocent growth. This may be due to the fact that, owing to local anatomical conditions, the tumour grows unequally, forming outlying lobules often attached to the parent growth by fragile connections; these may be torn through in removal, leaving a remnant to continue its growth. By the examination of large sections, including the greatest diameter, of fibro-adenomata of the breast, Cheatle has been able to demonstrate the presence of such subsidiary nodules within, or without, the capsule of many of these tumours.

Another source of the apparent recurrence of innocent tumours may be found in the occurrence of multiple tumours, one or more of which may have escaped observation at the time of operation. Multiple fibro-adenomata of the mammæ are frequently observed, and I have myself had the opportunity of examining a breast which illustrated this condition remarkably well. The breast presented an advanced condition of chronic mastitis, and contained a small cyst with a little intracystic papilloma, and from the naked-eye examination the papilloma appeared to have infiltrated through the wall of the cyst. On microscopic examination, however, the appearance of infiltration was found to be due to the presence of a second distinct cyst filled with papillomatous ingrowth; and several other similar, though microscopic, cysts were found in sections taken from other parts of the breast.

(*e*) **Ulceration.**—As a diagnostic sign, ulceration is of little value; it is frequently absent in malignant tumours and may be present in innocent ones, though in the latter case the tumour has usually attained a much greater size than in the former. In the case of non-malignant neoplasms ulceration will take place when the covering skin or mucous membrane is stretched by the mass of the growth, or when it is exposed to injury; and, in point of fact, both factors are usually present. In malignant neoplasms not only are the mechanical factors concerned, but there is usually a direct invasion and destruction of the tissues by the malignant cells.

(*f*) **Tendency to Central Degenerative Changes.**—Here again we have a sign which is of comparatively little importance, though it may indicate a considerable rapidity of growth. We have seen that a malignant growth obtains its nourishment from the new-formed vessels of the stroma supplied by the host, and it is easily understood that such a stroma requires a certain amount of time for its formation. Should the tumour be a very rapidly growing one, the stroma will be imperfect, and there will be an indifferent blood supply to the central part, with the result that necrosis of tissue will occur.

But degenerative changes other than necrosis may occur, and in tumours of a low grade of malignancy. Thus, myxomatous degeneration of a fibrosarcoma is of frequent occurrence and may be so advanced as to affect the greater part of the tumour, converting it into a mass of jelly-like consistence enclosed in a thin shell of tissue, though it is common knowledge that such tumours are not of a highly malignant nature.

(*g*) **Occurrence of Cachexia and Anæmia.**—In most advanced cases of malignant disease, and occasionally in quite early cases, the patient loses strength, becomes very emaciated, and presents a peculiar yellowish appearance of the skin ; and there is usually a more or less advanced degree of anæmia. It is to this syndrome that the name of cachexia is given, and it has been a matter of some debate as to whether the symptoms are due to the presence of the malignant growth or not. In tumours of the alimentary tract where there is direct or indirect interference with nutrition, cachexia is of early occurrence and is often extreme, but tumours of the breast and other regions protected from external contamination may attain quite massive proportions without giving rise to any constitutional disturbance.

In this connection it is interesting to note the observations of Bashford, Murray, and Cramer on tumour-bearing mice. They found that mice might bear enormous tumours without showing any sign comparable to the cachexia seen in human beings, and this even when metastases had formed ; but ulceration of the surface of the tumour, with hæmorrhage and septic infection, resulted in emaciation and the rapid death of the animal.

There is no doubt that the symptoms of cachexia are often the result of the bacterial invasion resulting from superficial ulceration of a tumour, but the possibility of a chronic intoxication with its metabolic products, or the products of its

necrobiosis, must not be lost sight of. It has been pointed out that many tumours exhibit an attempt at functional activity, and these secretions may even be the cause of the condition.

The blood changes in malignant disease are not characteristic. When present, they consist of an anæmia of the secondary type, varying greatly in its severity. In carcinoma of the stomach, and of the alimentary tract generally, it may be profound, but for the most part the alterations appear to be the result of a secondary infection. In severe cases, especially in carcinoma of the stomach, the blood picture is not unlike that of pernicious anæmia except that the hæmoglobin content is lowered. The red cells show variation in size and shape, poikilocytosis may be present, and there is usually a considerable degree of polychromatophilia; nucleated red cells are not common. The white cells show little change beyond a moderate leucocytosis in cases of secondary ulceration.

(*h*) **Power of Continuous Growth.**—Experimental studies have demonstrated that this is probably the most important attribute of malignant growths. Tumours which histologically show little or no deviation of structure from the parent tissues, and present none of the signs described above, are yet capable of unlimited propagation. While this fact is of the greatest importance in the theoretical consideration of malignancy, it is of little value from the standpoint of diagnosis in human cancer.

MULTIPLE TUMOURS

The simultaneous occurrence of two or more entirely different neoplasms in the same individual is so unusual as to excite attention, but it is a perfectly well recognised phenomenon, of which many instances have been put on record. The tumours may be innocent or malignant, of the same or different types, and situated in the same or different systems of the body.

The importance of the condition lies in the bearing it may have on the etiology of tumours in general, and in the possibility of the different neoplasms having more than an accidental relation to one another. The upholders of the "cell-rest" theory of the origin of cancer have seen in this phenomenon support for their views, for where there is one congenital abnormality there may well be another. Others who postulate some constitutional disturbance, or a generalised lowering of resistance,

as essential for the formation of a neoplasm, quote the concurrent growth of two tumours as evidence of such a change. Both claims, however, break down on examination.

Of much greater significance are recent observations which show that the presence of one malignant tumour in an individual actually inhibits the development of a second one (*vide* p. 58). The importance of these observations is obvious. If substantiated by further work, they indicate clearly the presence of a profound constitutional change in the individual, brought about by the growth of the tumour, a very different thing from the hypothetical constitutional change which has been suggested as the cause of the development of tumours. The fact that multiple tumours do occur does not negative this conception, for they are comparatively rare, and, moreover, one would hardly expect a biological inhibition of this nature to be invariably and uniformly potent.

The demonstration of a sarcomatous transformation of the stroma which occurs in the course of the propagation of certain carcinomata of the mouse raises the question of the relationship of multiple tumours to each other. Many of these tumours in the human subject are, anatomically, widely separated, and can only influence one another indirectly. But occasionally two tumours of different types occur in the same organ, and the possibility of the one providing the stimulus for the growth of the other immediately presents itself. So far, in spite of some suggestive observations, nothing definite can be said on this point.

It is scarcely necessary to insist that before a diagnosis of multiple tumours can be made, it is imperative that a thorough and critical microscopic examination be carrried out, in order to make certain that absolutely distinct neoplasms really exist.

RETROGRADE CHANGES

Neoplasms are peculiarly liable to undergo forms of degeneration, and it is rare to find a tumour of any size which does not exhibit retrogressive changes to a greater or less degree.

These have been ascribed to the rapidity of growth of the tumour cells, to their imperfect powers of assimilation, and, in the case of metastases, to alterations in the food supply consequent upon a foreign environment.

The most important factors would seem to be the inadequacy of the vascular and lymphatic supplies. Owing to its rapid growth, the formation of the nutrient vessels of the tumour fails to keep pace with the development of the parenchyma cells, and it is only at the periphery that sufficient nourishment is obtainable. Similarly, the imperfect lymphatic system renders the removal of the products of the cell metabolism an impossibility. Consequently we find the most marked changes occurring in the central parts of the more rapidly growing tumours, where a combination of insufficient nourishment and stagnation of metabolic products exists.

Fatty degeneration is one of the commonest forms to occur in tumours. It is associated with an imperfect blood supply and an anaplastic type of cell. It is therefore especially prone to appear in rapidly growing medullary or encephaloid cancers, though it may be seen in sarcomata and in innocent connective tissue and epithelial growths. It is a constant feature of hypernephromata, the cells of which are usually loaded with fat.

With ordinary methods of preparation, tumour cells often present a vacuolated appearance due to the solution, in the process of fixation and embedding, of the glycogen with which they were infiltrated. This **Glycogenic Infiltration** can scarcely be deemed a retrogressive change, but is rather in the nature of a reserve food supply. It was formerly supposed to occur only in tumours derived from adrenal tissue, but further research has proved this view to be erroneous for it can be demonstrated in many different types of growth.

Mucoid degeneration is quite common both in epithelial and connective tissue tumours. In epithelial tumours it usually affects the parenchyma and is a true cellular degeneration, but it may appear in the stroma, in which case the mucin is laid down in the matrix or intercellular substance; and the two forms may be combined. Both innocent and malignant epithelial tumours may undergo mucoid degeneration, but the carcinomata of the stomach, large bowel, and breast are chiefly subject to it. The term "colloid cancer" for such tumours, though in general use, is of course a misnomer, for the degenerative product is a true mucin and has nothing to do with colloid as we know it in the thyroid gland.

From what has been said on the subject of anaplasia, it might be supposed that in a mucus-secreting epithelium, such as that

of the rectum, the most advanced mucoid degeneration would occur in growths of a low grade of malignancy, since the production of mucus is an expression of the " work activity," as opposed to the growth of the cell. In point of fact, this is not necessarily correct, and the most pronounced mucoid degeneration I have seen in any tumour was present in a rapidly fatal carcinoma of the rectum, with very widespread metastases, in a youth of seventeen years.

Advanced mucoid degeneration, then, may be found in both innocent and highly malignant tumours, though whether the process is identical in each case is open to question.

Cystadenomata of the ovary frequently show what is known as mucoid degeneration, but in these tumours the substance formed is a pseudomucin, and does not give the chemical reactions of true mucin.

In connective tissue tumours the mucin is laid down in the matrix, and the cells of the growth are widely separated from one another. In this way are produced such mixed tumours as the myxofibromata and the myxochondromata. Among the malignant neoplasms of this class it is, as a rule, only in the slow-growing fibrosarcomata that mucoid degeneration takes place.

Hyaline degeneration is seen in the stroma of slow-growing connective tissue tumours, especially the fibromyomata. It is also occasionally found in epithelial tumours, the individual cells of which become converted, entirely or in part, into masses of homogeneous hyaline material. These bodies may lie free among the cells of the tumour, or, if the cell concerned has not undergone disintegration, they may remain embedded in the cytoplasm, and they are of some importance since they have frequently been mistaken for forms of a cancer parasite.

Hæmorrhage into the substance of a tumour usually follows the rupture, either spontaneous, or the result of trauma, of one of its own vessels. It most often occurs in sarcomata, since in these tumours the vessels are ill-formed and supported by little more than the tumour cells, and are consequently unable to bear any considerable strain.

Necrosis may be quiet (necrobiotic) or inflammatory in nature. In the first case it results from insufficiency or obliteration of the blood supply to the part of the tumour concerned, and though the parenchyma is usually alone affected, large areas of parenchyma and stroma may necrose *en masse*. In

encephaloid carcinomata, the central portions of the alveoli are often necrotic, while the peripheral cells, in closer relation to the nutrient vessels of the stroma, remain healthy and retain their staining reactions.

As the result of quiet necrosis large areas of a tumour may be converted into a cheesy material resembling the caseation of a tuberculous lesion; or, again, the necrotic material may liquefy with the production of pseudocysts.

When invaded by bacteria, tumours, especially those on the surface of the body, frequently undergo acute inflammatory necrosis with the production of offensive discharges and sloughing.

As has already been pointed out, the cachexia of cancer is largely due to necrosis of the tumour and the consequent absorption of the products of cell destruction.

Calcification, or **Calcareous degeneration,** commonly follows extensive necrosis. It is irregular in its distribution, though it usually affects the centre or a thin peripheral zone of the tumour. Connective tissue growths, fibromas and myomas in particular, are peculiarly liable to it, and in a more limited degree it is not uncommon in epithelial growths. Small calcareous bodies are also a prominent feature in such tumours as the psammoma and the psammo-carcinoma, and in these there is often a primary deposition of calcium salts without any previous necrosis.

Just as **Ossification**, or true bone formation, may occur in calcified inflammatory foci, so it may appear in necrotic and calcified tumours. Nicholson[1] has studied the formation of bone in a calcified epithelioma of the skin, and has reviewed the literature on the subject.

Finally, in certain tumours, of which the atrophic scirrhous carcinoma of the breast is the best example, there is an excessive production of fibrous tissue in the stroma. This **fibrosis** is not to be looked upon as a retrograde change in itself, but merely as an indication of the chronicity of the growth.

DISSEMINATION

Sooner or later every malignant tumour spreads beyond its site of origin and invades other tissues of the body, producing metastases, or secondary growths.

[1] *Journal of Path. and Bact.*, vol. xxi. p. 287.

We have seen that in the course of its growth, a malignant neoplasm invades and destroys the tissues in its immediate neighbourhood; but, apart from this process of infiltration, we find secondary growths developing in parts of the body remote from the primary tumour, and separated from it by apparently healthy tissue. It is to such manifestations that the name ***metastasis*** belongs.

There is, of course, a superficial resemblance between this dissemination of a malignant growth and the extension of the inflammatory process encountered in infectious conditions such as staphylococcal pyæmia, or tuberculosis. In both there occurs a primary focus of disease from which are derived secondary foci throughout the body; but it is scarcely necessary to point out that the formation of the secondary manifestations is entirely different in the two cases. In an infective condition, the infecting agent, staphylococcus, tubercle bacillus, or other organism, is transported to different organs of the body, where it causes a reaction of the tissues of the part and attracts wandering cells from the blood stream, the resulting focus being composed of a mixture of various elements. In malignant disease, on the other hand, the secondary nodule is formed by the lodgment and subsequent proliferation of tumour cells which have become separated from the parent growth, the fixed cells of the affected tissue and the wandering cells playing only a subsidiary part in the formation of the metastasis.

Generally speaking, a malignant growth breeds true; that is to say, its secondary growths reproduce the features of the tumour from which they arose. But this rule is not absolute: often enough the histological characters of the primary and secondary growths show differences which are sometimes quite marked. On the one hand, the metastasis may be apparently more benign in its character, growing expansively and compressing the surrounding structures rather than infiltrating them; or the tumour may become more virulent as it disseminates, and the cells of the daughter nodules may assume a much more embryonic type than those of the parent growth. So it frequently happens that the metastases of a spheroidal-celled carcinoma simplex of the mamma assume an acinous type of formation, or an intensely scirrhous carcinoma of the breast gives rise to encephaloid metastases in the axillary glands and elsewhere. Such variations are usually to be explained by a

consideration of the structure of the organ in which the metastasis occurs. Loose, lymphadenoid tissue, for example, offers an extremely favourable nidus for the development of the malignant cells, and the study of small deposits in these and similar situations often throws a great deal of light on the nature of the primary tumour. In some instances, however, there seems to be no doubt that the virulence of the tumour cells increases with their dissemination.

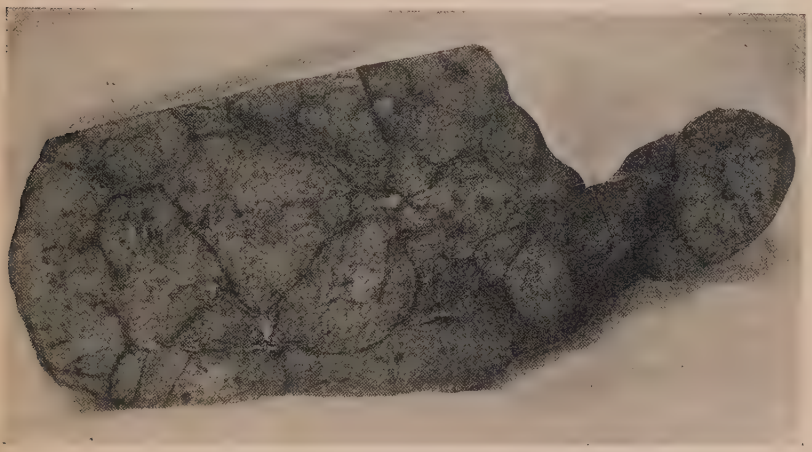

Fig. 3.—Section of liver showing many large metastatic tumours secondary to the carcinoma of the colon illustrated in Fig. 4.

Metastases exhibit an extraordinary degree of variation in size, number, time of appearance and clinical importance in the different classes of tumours, and in similar tumours of any particular organ.

Occasionally, the secondary growths may dominate the clinical picture, the primary tumour being insignificant both in its size and in its local effect; indeed, the size of a malignant tumour bears no necessary relationship to the size or number of its metastases. Thus, I have performed an autopsy on a case in which the only possible clinical diagnosis was "malignant disease of the liver." That organ was enormously enlarged, weighing 119 oz., and was filled with metastatic growths which had destroyed the greater part of the gland (Fig. 3). Only after careful search was the primary tumour revealed in a small, flat

carcinoma of the pelvic colon, half an inch in diameter (Fig. 4). There was some slight involvement of the mesentery opposite the affected portion of the bowel wall, but no deposits were found in any of the other organs.

Every pathologist could supply instances of such cases, but, as a rule, the primary tumour is larger than any one of its secondary growths.

FIG. 4.—Pelvic colon opened to show a small flat carcinoma (A) which gave rise to large secondary deposits in the liver (Fig. 3).

In some cases, vast numbers of metastases are found at the post-mortem examination, involving almost every organ; many of them are quite small, so that it seems as if an acute dissemination had taken place during the last weeks of life. In other cases, there may be no remote dissemination, the spread of the growth being entirely by a process of infiltration.

The position in which secondary foci develop is a point of very considerable interest. The metastases of various tumours show a remarkable tendency to appear in certain tissues or organs, while other situations seem to be almost immune to secondary deposits from any form of growth. We know from experience that in all forms of carcinoma involvement of the neighbouring

lymphatic glands is usually present; growths of the alimentary canal often give rise to metastases in the liver, and the bones are commonly affected in tumours of the thyroid and prostate glands. Other organs, such as the kidney, pancreas, and brain, are less frequently involved, and even in extreme dissemination metastases are rare in the spleen, the intestines, and the skeletal muscles.

Though such peculiarities may often be explained by anatomical or mechanical considerations, we are faced by the fact that certain tissues appear to offer an unusually favourable nidus for the metastases of particular tumours; they are, in fact, ***tissues of predilection.***

Sampson Handley, in his exhaustive study of dissemination in cancer of the breast,[1] has demonstrated that the bony deposits so often met with in this condition are but a part of the general permeation of the body which extends, in ever-widening circles, from the primary growth. But such a process will not explain the extraordinary number of metastases found in the bones in cancer of the prostate, where deposits in the soft parts may be limited to the lumbar lymphatic glands, whilst the bones, including those of the skull, may be riddled by them. Again, the liver, receiving the blood from the portal system, is likely to be affected in tumours of the intestine; but this is no reason why it should be so commonly involved, as it is, in melanomata of the skin and the eye. On the other hand, the apparent immunity to secondary growths exhibited by the spleen, the intestines, and the skeletal muscles is probably to be explained by the fact that they are constantly contracting. They may be directly infiltrated or permeated by columns or masses of growth, but they offer highly unfavourable conditions for the lodgment of small malignant emboli.

A question of great importance is that of the period of the disease at which secondary manifestations appear. Some tumours disseminate with appalling rapidity, so that within a few weeks of the recognition of their presence such extensive metastases occur as to render surgical interference quite hopeless. In other cases, dissemination is slow and limited in extent, and complete removal of the affected organ with the secondarily affected area may result in cure. But in such circumstances a considerable interval of time must elapse before a cure can be claimed, and

[1] *Cancer of the Breast*, London, 2nd edition, 1922.

for this reason : metastases may remain latent in the tissues for long periods though still retaining their vitality. Cases have been recorded in which twenty, or even thirty, years elapsed after the removal of the primary tumour before secondary manifestations appeared. These cases are, of course, exceptional, but it is quite common for secondary growths to appear two or three years after the removal of the original tumour. No theory is adequate to explain how the seeds of such metastases can remain latent for so long a period, retaining their vitality and maintaining their footing in a strange soil, or why they should suddenly assume an excessive proliferative power ; but the fact remains, that no case of cancer can be considered to have been cured by an operation until at least three years have elapsed without signs of recurrence, and even then the prognosis is little more than favourable. It may be that local recurrence is not always metastatic, but sometimes of the nature of an entirely fresh growth ; the influence which gave rise to malignant change in the cells of an organ may still be potent to affect any remains of that organ which may have been left undisturbed at the time of operation. I have, for instance, examined an undoubtedly malignant papilloma occurring on the dorsum of a tongue, part of which had been removed for malignant growth fourteen years before ; the growth had all the appearances of being a primary one, and the possibility of its being a secondary one was almost negligible.

An operation for the cure of cancer can only be successful when the whole of the growth is removed ; if a single metastasis is overlooked, the proceedings are doomed to failure. So, if surgical measures are to be of any value, it follows that the spread of the growth must be of limited extent. Further, it is essential that the operator should be acquainted with the modes or paths of malignant dissemination if he is to plan his excisions so as to include zones of probable infection.

The process of local infiltration is well understood. It consists essentially of an extension of the growth in lymphatic spaces and along fascial planes ; in fact, extension along the lines of least resistance (Figs. 5 and 6). But the explanation of the formation of remote metastases is more difficult, and is complicated by the fact that, as a centre of dissemination, every secondary deposit may behave as a primary growth. In this way the paths of infection in any particular case are often

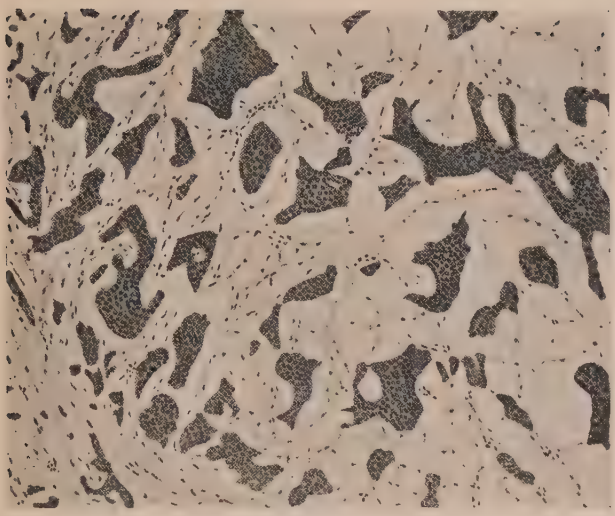

FIG. 5.—Section from the growing margin of a carcinoma simplex of the breast. Groups of carcinoma cells infiltrating fatty tissue.
Obj. 16 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

FIG. 6.—From a carcinoma simplex of the breast. Groups of malignant cells (1) infiltrating between muscle fibres (2).
Obj. 16 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

obscured; and the obscurity may be deepened by the simultaneous occurrence of two or more processes of extension.

For practical purposes three methods of dissemination may be distinguished:

1. Transplantation.
2. Permeation.
3. Embolism.

1. Transplantation

Several varieties of dissemination may be distinguished under this heading; they include all those forms which essentially take place without the aid of lymph or blood vessels.

(*a*) **Transplantation by Apposition.**—This method is by no means of frequent occurrence. It consists in the infection of a surface by actual contact with a malignant growth, and there must almost certainly be some abrasion of the infected surface for the successful lodgment of the malignant cells to take place. Instances which may be encountered are the transference of growth from a carcinoma of the lip to the other lip, and of carcinoma of the cervix uteri to the wall of the vagina. Cells from an extensive carcinoma of the breast may become grafted on to the patient's arm should that limb be fixed to the affected side from one cause or another, and I have seen such transference take place into the incisions made for the insertion of silk drains in a case of brawny œdema of the arm. Under the heading transplantation by apposition, we may include those cases of dissemination in a hollow viscus, the most obvious example being found in the villous papilloma of the urinary bladder. Here, contact between the tumour and the bladder wall results in the formation of a secondary tumour, and so the condition spreads until a considerable number of tumours are present on the wall of the viscus.

In this division may be grouped those rare instances of transplantation occurring in the alimentary canal, where a nodule of growth may become attached to, and grow in, the wall of the canal below the primary tumour. In these cases it is difficult or impossible absolutely to exclude dissemination by embolism or permeation, or even the occurrence of multiple primary tumours, and it is by no means easy to understand how successful transplantation can take place; but I have encountered what I believe to be true examples of implantation, on to the wall

of the œsophagus from a squamous carcinoma of the tongue, and on to the wall of a gastric ulcer from a carcinoma of the œsophagus.

(*b*) **Transplantation in Serous Cavities.**—Should a malignant growth burst through the lining membrane into a serous cavity such as the peritoneum or the pleura, it is easy to understand how small groups of cells, separated from its surface, may

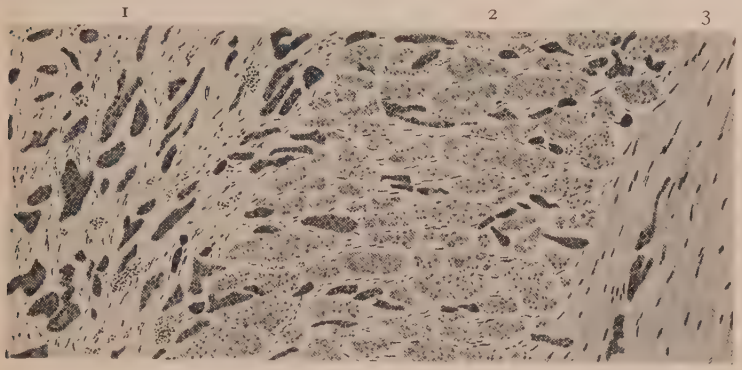

Fig. 7.—Carcinomatous dissemination in the peritoneal cavity. Section of vermiform appendix showing malignant invasion of the wall from without inwards—secondary to carcinoma of stomach. (1) Serous coat; (2) outer muscular coat; (3) inner muscular coat.

Obj. 16 mm. apochrom. Comp oc. 4. Tube length, 160 mm.

be planted on to the membrane in the immediate neighbourhood of the tumour, or transported to distant parts of the cavity by the movements of the contained viscera. Having once obtained a footing, they will proliferate and give rise to definite metastases (Fig. 7). Such a mode of spread is well seen in ovarian tumours and certain growths of the stomach, especially the "colloid" carcinoma. Sampson Handley would lay great stress upon this process in the spread of carcinoma of the breast when the malignant cells permeate the chest wall and enter the peritoneum at the epigastric angle. This process may be, and commonly is, associated with permeation of the subserous lymphatics, and in cases of advanced malignant invasion of the peritoneum or the pleura many of the nodules of growth are outcrops from the permeated lymphatics, and are not true examples of transplantation.

(*c*) **Inoculation.**—The experimental study of cancer has demonstrated the ease with which auto-inoculation, the inoculation of a tumour-bearing animal with particles of its own tumour,

may be performed. So it is not surprising to find a similar process occurring in malignant disease in the human being. If, in the course of its removal, a malignant growth be opened, there is a grave risk of escape of groups of the tumour cells into the exposed tissues of the wound, the probable result being an early local recurrence ; and it is quite certain that a scalpel or needle,

Fig. 8.—Inoculation of carcinoma into the skin of anterior abdominal wall. (1) Columnar-celled carcinoma ; (2) superficial epithelium.
Obj. 16 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

contaminated by contact with the growth, may be the means of conveying the infection. Sir Bernard Spilsbury kindly allows me to quote the following case in illustration of this process. An abscess of the liver was suspected in a patient who presented an anomalous enlargement of that organ, and the tumour was explored with syringe and needle by the house physician. No fluid was withdrawn, but in the bore of the needle Spilsbury detected a small shred of tissue ; he was able to prepare sections of this, and found it to be a fragment from an adenocarcinoma.

The patient was discharged, but returned to the hospital some time afterwards, coming under the care of the same house physician, who noticed a small nodule in the skin of the anterior abdominal wall at the site of the previous exploratory puncture. This nodule was excised, and examined by Spilsbury ; it was a nodule of adenocarcinoma (Fig. 8). Later, the patient died, and at autopsy a primary adenocarcinoma of the liver was revealed.

2. Permeation

The recognition of this mode of spread is due to the researches of Sampson Handley. As the result of his extensive investigations into the spread of cancer of the breast, he came to the

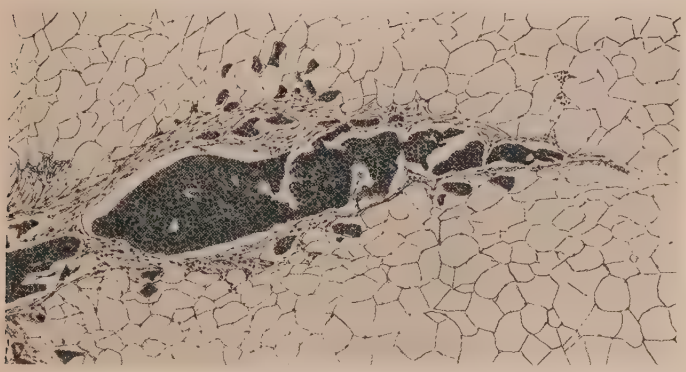

Fig. 9.—Section from periphery of a carcinoma simplex of the breast showing permeation of a lymphatic vessel by carcinoma cells.
Obj. 16 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

conclusion that the vast majority of metastases are due to a process which he termed lymphatic permeation. By this term is meant the gradual extension of the outlying processes of the tumour, in the form of solid plugs or columns, into and along the larger lymph vessels (Fig. 9). As the result of the distension of the vessel thus produced, the wall becomes stretched and eventually bursts ; but before the stage of rupture is reached a perilymphatic reaction or inflammation, consisting in a proliferation of fibroblasts and an accumulation of round cells, is usually evident, which reaction becomes more intense, with the final result that the cancer cells are choked and killed. Extension of growth, however, proceeds at the distal end of the plug, and so it comes about that a solitary nodule may develop at some

distance from, and apparently unconnected with, the primary tumour. Sampson Handley does not deny that embolism may play a part in the dissemination of malignant growths of the breast, but he insists, and rightly, that permeation is the major process. Further, this investigator has shown that permeation occurs by choice in lymphatics of not less than 40-50 μ diameter, avoiding the smaller vessels and the larger trunks where the force of the stream is sufficient to sweep the cells away as emboli.

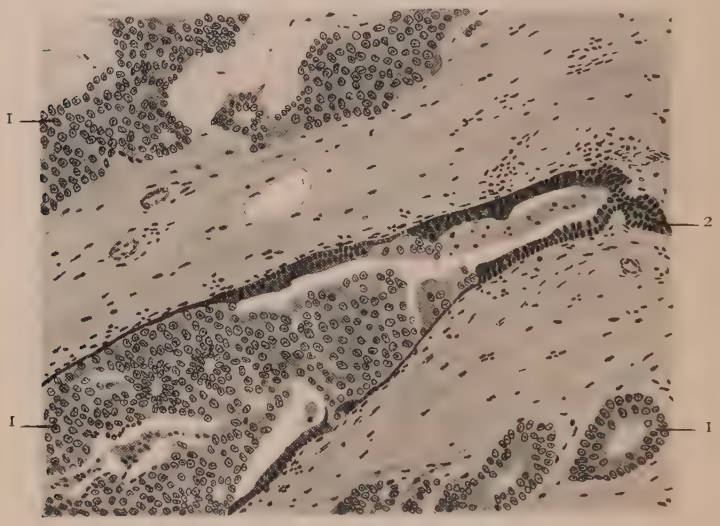

FIG. 10.—Section of a carcinoma of the breast showing permeation of a duct.
(1) Carcinoma ; (2) duct-epithelium.
Obj. 8 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

Superficially, the process of permeation thus described closely resembles the infiltration which is such a distinctive feature of malignant tumours ; but, as Handley points out, the two are distinct and differ in important particulars.

Infiltration takes place in tissue interspaces, is the earliest disseminative process, and is best seen at the macroscopic growing edge ; permeation occurs later, is limited to lymphatic vessels as opposed to lymph spaces, and is best seen in the microscopic edge of growth often six inches from the apparent margin of the tumour.

Infiltration is a slow process, since the tissue spaces are small and often interrupted ; permeation is comparatively rapid, the

larger channel offering less resistance to the advancing column, and is therefore by far the more important.

The two processes are, of course, interchangeable. Infiltration will occur round the secondary nodules resulting from permeation, and infiltrating cells will spread by permeation should they chance to invade a lymphatic vessel. It becomes obvious, therefore, that the study of the anatomy of the main and subsidiary

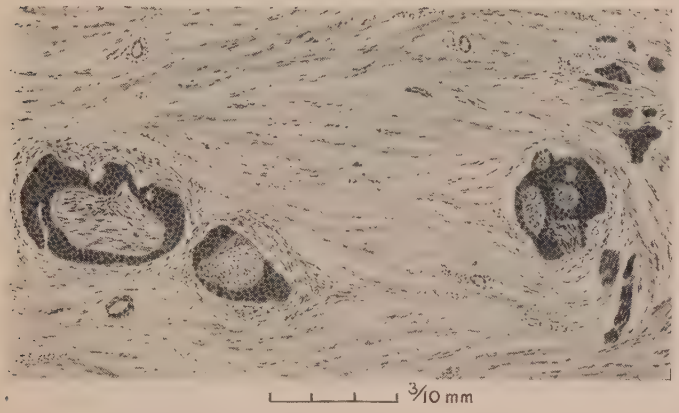

Fig. 11.—Nerve invasion in carcinoma of the uterus. Section of the parametrium showing permeation of the perineural lymphatics by columns of carcinoma cells.

lymphatic systems of the body is of the highest importance to the operating surgeon, for only by recognising the probable paths along which permeation will take place can he plan his operations with any hope of success.

Although permeation occurs chiefly along lymphatics, it must not be forgotten that it may take place along veins or ducts (Fig. 10), though rarely to any great extent. The most frequent examples of venous permeation are seen in cartilaginous tumours, and the most famous example is the malignant Testicular Chondroma of Paget, afterwards described as a carcinoma by Kanthack and Pigg [1] and a teratoma by Nicholson,[2] where the growth permeated the spermatic vein, eventually entering the vena cava. An interesting form of permeation is that occurring in the lymphatics of nerve trunks. There is some evidence to show that this form of dissemination may be of considerable clinical importance (Fig. 11).

[1] *Trans. Path. Soc. Lond.* vol. xlviii. [2] *Guy's Hospital Reports*, vol. lxi.

3. Embolism

Until within comparatively recent years, embolism was regarded as being the only method by which widespread dissemination of malignant growths could take place. It was the most natural and obvious explanation, and was borne out by the frequent involvement of lymphatic glands, and the observation, in tissues preserved at the post-mortem examinations of patients dying from malignant disease, of small emboli of cancer cells lying in the capillaries of various organs.

In the embolic theory it is supposed that small groups of tumour cells find their way into the venous or lymphatic circulation, usually by direct invasion of the walls of the radicles in the immediate neighbourhood of the tumour, and are carried along in the circulating stream until they become arrested in a capillary system, where they take root and develop into daughter nodules.

In the malignant tumours of connective tissue origin, where the parenchyma cells are in close contact with the blood vessels, often indeed replacing the vascular endothelium, embolism is even now regarded as of primary importance in dissemination, but in the carcinomata there have always been difficulties in the complete acceptance of this theory.

In the first place, embolism should be universal throughout the body, and the distribution of the resulting metastases should be more or less uniform. But, as Paget has shown,[1] this is far from being correct.

Then again the lungs, containing as they do the first capillary system in the systemic circulation through which venous blood flows, should frequently be the site of secondary growths ; for it is scarcely likely that all malignant emboli are sufficiently small to pass through the pulmonary capillaries to reach the left side of the heart. And yet the lungs are often apparently free from such deposits when other organs are affected. As a matter of fact, Schmidt [2] has demonstrated that such pulmonary emboli are of very common occurrence but are usually ineffectual, since they become surrounded by a thrombus, which, undergoing organisation, destroys or successfully encapsules them.

To explain these anomalies various subsidiary theories have been formulated, such as that of ***Tissue Predilection*** and the

[1] *Lancet*, 1889. [2] *Die Verbreitungswege der Karzinome*, Jena, 1903.

occurrence of ***Retrograde Embolism.*** The former has already been referred to and requires no further discussion. Retrograde Embolism consists in the passage of an embolus in the reverse direction to the circulating current. It can only take place if there is a negative pressure in the vessel concerned, and must be extremely rare.

Finally, the elaboration of the doctrine of lymphatic permeation, and the strikingly successful results which have followed

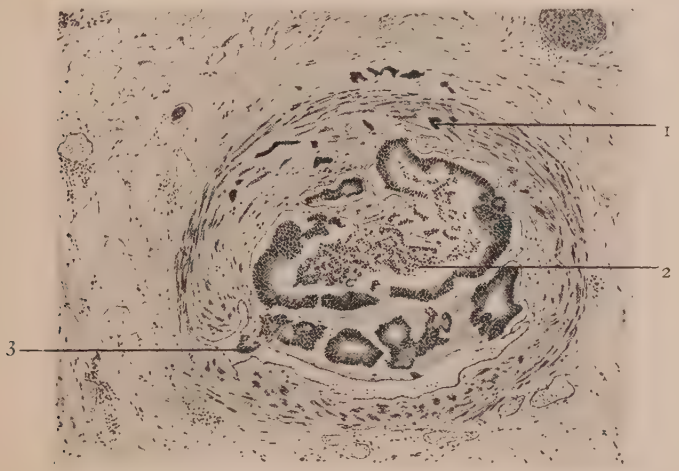

FIG. 12.—Section of a mesenteric vein invaded by carcinoma of the pelvic colon. The tumour cells have invaded the wall of the vein (1), and have proliferated extensively beneath the endothelium (2); groups of cells have burst through the intima and lie free in the lumen (3).

Obj. 16 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

its application in operative procedures in malignant disease of the breast, have tended to relegate embolism to a position of very minor importance.

Nevertheless there can be no doubt but that this mode of spread may be a very potent factor in malignant dissemination. It is acknowledged that emboli are of frequent occurrence; they may constantly be seen lying in capillary vessels, and, much more rarely, the infiltration of the veins in the neighbourhood of the tumour may be observed (Fig. 12). What is disputed is the frequency with which such emboli retain their capabilities of growth in suitable situations.

It is, of course, extremely difficult to demonstrate the lodgment and growth of a malignant embolus. By the time that a

metastasis has attained macroscopic proportions, the normal histology of the part is entirely lost, and it is impossible to prove that invasion of the tissues occurred from inside a vessel and not from the perivascular lymphatics. True, in the experimental study of cancer, serial sections of the lungs of mice have demonstrated beyond cavil the invasion of these organs by way of the pulmonary artery. But in the human subject the preparation of such illustrative sections must always be a matter of chance.

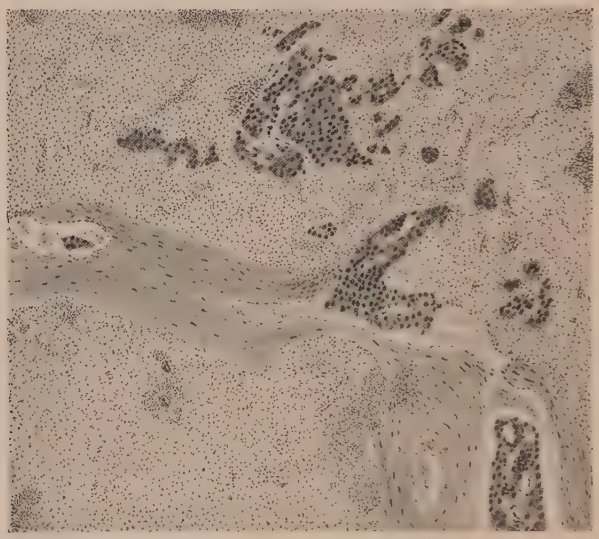

FIG. 13.—Vascular dissemination in the spleen, secondary to carcinoma of the breast. Masses of carcinoma cells lying in the spleen pulp, and in a large vein; a large column of cells can be seen passing into the vein.
Zeiss Obj. aa. Comp. oc. 6. Tube length, 160 mm.

However, in certain observations on secondary growths in the spleen,[1] I have shown that malignant cells may lie in the spleen pulp without giving rise to any reaction on the part of the blood, and may find their way into the portal circulation by the splenic vein (Fig. 13).

In the lymphatic system, the microscopical evidence for embolism is stronger. The involvement of lymph glands with no microscopic lesion in the surrounding connective tissue may constantly be observed; and all stages, from the appearance of isolated clumps of tumour cells in the lymphatics at the

[1] *Journal of Pathology and Bacteriology*, vol. xvii. (1912).

hilum and in the marginal sinuses, to complete destruction of the gland, may be followed. Even when there is distinct permeation of the vessels leading to the invaded gland, it is quite possible that embolic infection of the gland is primary and that retrograde growth along the afferent vessels has taken place.

Whether the microscopic evidence for embolic dissemination be accepted or not, the naked-eye findings often offer overwhelming proof that this process has taken place. But it is erratic and, apparently, occurs somewhat late in the disease; and, provided that the possibility of it is always kept in mind, the surgeon's attention must be chiefly devoted to the process of permeation.

ETIOLOGY

The question of the etiology of tumours is probably the most difficult and important problem in the whole of pathology. Certain etiological factors have become well recognised, but the essential cause of the uncontrolled proliferation of cells characteristic of all neoplasms is as obscure now as when the study of the subject was first approached. It is by no means certain even that there is one essential cause, and many authorities are prepared for the recognition of different determining factors in different classes of tumours, especially in such widely separated groups as the innocent and the malignant.

For the present, however, it is generally assumed, as a basis for investigation, that the etiology of all varieties of tumours is the same, and naturally chief attention has been devoted to the causation of malignant growths.

Before discussing the various theories which have been advanced from time to time to explain the occurrence of tumours, it would be as well to consider those more general conditions which might be expected to exercise influences of a varying degree of importance.

It must be recognised that the available statistics bearing on these conditions are far from satisfactory. The records of the Registrar-General are imperfect, since the majority of the diagnoses rest upon clinical evidence alone; and while hospital figures are more reliable, they contain another source of error in that they refer to a somewhat restricted class of the community.

However, as the result of careful investigation, certain facts may be regarded as having been definitely established.

Age.—Some classes of tumours show a definite age distribution ; but variations frequently occur, and it is only possible to make a few broad generalisations under this heading.

With the exception of a few congenital neoplasms, certain sarcomata, and such innocent connective tissue growths as the chondromata, it may be said that tumour formation is rare before adolescence. After this period there is an increasing liability to both the innocent and the malignant forms up to about the age of 55, when they gradually become less frequent.

The great majority of carcinomata occur between the ages of 35 and 65, the optimum age for men being 55 and for women 50.

It was formerly believed that sarcomata appeared mainly in children and young adults ; but this is not the case, for recent figures show that the age incidence of this class of tumour resembles that of the carcinomata, increasing up to the age of 55, and then diminishing by degrees. Sarcomata, however, certainly differ from carcinomata in that a far greater proportion occur before the age of 25.

Sex.—Cancer occurs more frequently in women than in men, in the proportion of three to two. Thus, in the years 1901 to 1903 inclusive, the deaths from malignant disease in England and Wales numbered 33,788 among males and 50,660 among females.

An analysis of the sites of origin of the growths shows that the difference is due to the large proportion of cases of malignant disease of the female genitalia ; with a few comparatively unimportant exceptions, other organs show much the same incidence in the sexes.

Tables for these years give the following organ distribution [1] :

	Males.	Females.
Breast	61	8,367
Uterus	..	11,714
Ovary	..	920
Stomach	7,349	7,119
Intestines	2,385	3,338
Rectum	3,450	2,939
Bladder and urethra	1,068	483
Kidney and suprarenal	350	396
Tongue	1,837	249
Brain	367	286

[1] *Second Scientific Report, Imperial Cancer Research Fund* (Part I.). Part II. of the same report contains a valuable discussion of the various cancer theories.

These figures are of value since they emphasise the liability to malignant disease of organs which, throughout life, are the seat of active cellular and vascular changes. For example, cancer is exceedingly rare in the male breast, and in men that organ is rudimentary and functionless; in the female, on the other hand, this form of tumour provides one-sixth of the fatal cases, and the gland is active, actually or potentially, throughout a long period, and is subject to important involution processes.

Heredity.—It frequently happens that two or more members of a family, either in the same or different generations, or both, die from malignant disease. The proportion of cases in which a cancerous ancestry exists varies considerably according to different observers, but some of the family histories on record are so striking in this respect that it is scarcely surprising that a belief in the importance of heredity in the etiology of tumours should be widespread. Nevertheless, there is no reliable evidence that such a relationship exists. Malignant disease is found in all parts of the country and in all classes of the community, and a large proportion of the population, one in eight of females and one in twelve of males, after the age of 35, succumb to it every year. As Bashford points out,[1] under these circumstances few large families can escape. In man, the difficulties of obtaining a sufficient number of reliable and controlled pedigrees are so great as to make the problem practically impossible of solution. But with the recognition of propagable tumours in such a short-lived animal as the mouse, a profitable field for research in this direction immediately became apparent. As the result of experiments in breeding from mice of known cancerous ancestry carried out through a number of years, Murray[2] has arrived at the following conclusion: "... Female mice, in whose ancestry cancer of the mamma has occurred not farther back than the grandmothers, are distinctly more liable to develop the disease spontaneously in this organ than those in whose ancestry cancer is more remote." But, as stated in the Introduction to the same Report, these figures must by no means be taken as applying to cancer in human beings, in whom such selective breeding can never occur except by accident.

Locality.—Analyses of the statistics of the cancer incidence in different parts of countries, or even of towns, seem to show

[1] Introduction, *Third Scientific Report, Imperial Cancer Research Fund.*
[2] *Fourth Scientific Report, Imperial Cancer Research Fund.*

that the disease is more prevalent in damp, low-lying districts than elsewhere. Further, these observations have been narrowed down so as to include actual dwelling-places, and several instances of "cancer houses," houses in which an unduly high proportion of cases of cancer have occurred, have been recorded. The bearing of these observations on the question of the infectivity of malignant disease is obvious, for if it can be shown that the inhabitants of a certain building are more prone to cancer than their neighbours, it is not unreasonable to assume that the fault lies in the house, and the presence of some external influence, possibly parasitic, becomes highly probable.

But before the evidence in favour of such cancer houses or districts can be accepted as at all conclusive, a much larger body of figures must be available, for to the errors of chance must be added those errors due to the confusion arising from the many factors, some hiddden, some apparent, which may influence the onset of the disease.

It might have been expected that with the facilities afforded by the experimental propagation of cancer, this question could have been definitely decided one way or the other. But even here diametrically opposed views are held by different observers. Borrel and others have noted the occurrence of epidemics of cancer in breeding establishments ; Bashford, on the other hand, states that no such epidemics have ever been encountered, either in his own laboratory or in the breeding establishments from which his stock is obtained, and he brings forward some very remarkable figures in support of his contention.

Civilisation.—It is customary to ascribe to what is vaguely known as civilisation most of the ills to which we are subjected, and cancer is supposed by many people to be a disease of civilisation. But the term is far too indefinite, and includes far too many factors to warrant its use in the serious study of cancer. If by civilisation is meant the direct opposite of barbarism or "wildness," then there can be no possibility of distinguishing between the incidence of malignant disease in civilised and uncivilised peoples. The ultimate diagnosis of cancer rests on a histological basis, its presumptive diagnosis on skilful clinical and post-mortem examinations. The uncivilised are outside the scope of these procedures. Even if by chance the presence or absence of cancer can be established in any particular barbarian, this means nothing in the absence of numerical data of the total population

and age distribution of large numbers of barbarians together with controlled statistics of the causes of death among them. The same, of course, applies to animals. We know that cancer occurs in domestic animals, and statistics of its incidence in animals bred in captivity, the mouse, for example, are available ; but it is impossible to say what proportion, if any, of the total population of lions dies from cancer. If, on the other hand, by civilisation is meant the mode of life peculiar to particular communities of individuals, then it may be pointed out that there exist at present many civilisations, and there have existed in the past very many more, all differing profoundly from one another in their manner of life, in their habits, their diet, their diseases, and so forth. While there is, therefore, no general factor which we can call civilisation, there are factors in different civilisations which undoubtedly predispose to cancer.

The origin of malignant disease has been so freely ascribed in recent years to two presumed concomitants of civilisation, auto-intoxication from intestinal stasis, and an improper dietary, that we may reasonably enquire with what justification.

The assumption that constipation is an evil of civilisation rests upon the slenderest basis. Constipation itself is a relative state ; what in one individual may be a recognisable degree of intestinal stasis, is in another a perfectly normal condition. While there is and can be no reliable data of the incidence of either malignant disease or intestinal stasis in uncivilised peoples, there is not even any evidence that the latter is peculiar to modern life. Probably the most intimate human record we possess is " Pepys's Diary," written some 270 years ago. From its pages we learn that Mr. Pepys found it necessary to assist nature constantly and with vigour, though no suggestion is vouchsafed that he regarded himself as otherwise than a normal individual. There is, in fact, no proof that constipation is a condition peculiar to our modern civilisation, nor is there any proof that it determines the origin of malignant disease. Indeed, from the vast sums of money spent every year in advertising aperient and purgative medicines, it would be as just to argue that cancer is associated with intestinal unrest, for it is difficult to imagine how any modern civilised intestine can remain static for any length of time.

The influence of diet on the origin of cancer is apparently negligible, though the disease occurs in races differing so widely

from one another in their diet that any food factor common to them all can hardly have escaped notice. Inasmuch as their action is manifested most clearly in young, growing animals, it has been thought that vitamins might play some part in the biology of tumours. The work of Cramer,[1] however, shows that they have no influence at all. He finds that neither a deficiency nor an excess of vitamins has any effect on the growth of tumours in experimental animals, nor do tumour-bearing animals in these experiments differ from the normal control animals in their reactions to the abnormal diets. There is, then, no specific relation between vitamins and malignant growths, and no experimental justification for methods of treatment which consist in altering the vitamin content of the diet.

To sum up, it has not been proved that civilisation has any influence on the origin of cancer. In the absence of reliable statistics it is impossible to make any comparison between the cancer incidence in civilised and uncivilised countries or races. Though figures are not available, malignant growths have been found in civilised and savage races all over the world, in races living under the most diverse conditions of climate, habit, diet, and so forth. Again, the zoological distribution of cancer is as wide; mammals, amphibians, and fishes are all affected, wild and domestic animals suffer alike.

Injury and Irritation.—Prolonged injury or irritation is a frequent forerunner of cancer, and is acknowledged to have an important etiological significance. A great variety of irritants capable of producing cancer if applied over a sufficient interval of time are recognised, but their mode of action is unknown.

The association of gall-stones with cancer of the gall-bladder is well known, and has recently been reproduced experimentally by A. Leitch; and cancer of the scrotum in sweeps is recognised as following the prolonged irritation of the skin by soot. Workers in paraffin factories suffer from cancer of the skin, and similar tumours have been described by Hutchinson as following the prolonged internal administration of arsenic.

An interesting form is the squamous carcinoma of the abdominal wall, occurring in the natives of Kashmir, which develops in the burns resulting from the custom of carrying the Kangri, an earthenware basket containing a charcoal fire, under the clothes in close contact with the skin.

[1] *Eighth Scientific Report, Imperial Cancer Research Fund.*

The same type of tumour is found on the shins of engine-drivers as the result of long exposure to the heat of the fires.

Before the dangers attendant on their application were realised, and the precautions necessary to take in order to avoid these bad results were fully understood, workers with the X-rays frequently suffered from a form of dermatitis, and in some cases this was followed by the appearance of squamous carcinoma in the affected area.

The chronic lesions of infective diseases may also be complicated by the development of malignant growths. This is seen in the occurrence of epithelioma in old-standing cases of lupus, and in the skin at the margin of old tuberculous sinuses, of carcinoma of the tongue in syphilitic leucoplakia, and of carcinoma of the bladder following Bilharzia infection.

The presence of other parasites in malignant tumours has been noted by several observers. Borrel, for example, has found a demodex in cancer of the skin, Haaland has encountered nematodes in breast cancers of the mouse, and Fibiger discovered a nematode in carcinomata of the stomach in rats. Further, by feeding rats with cockroaches infected with the worm, Fibiger has been able to produce the tumours experimentally.

Other examples of cancer following chronic irritation of one form or another might be quoted, but sufficient has been said to demonstrate the importance of this factor.

It will be noticed that these various irritants act continuously over long periods of time. Alexander Scott in his monograph on the Occupation Dermatoses of Paraffin Workers,[1] states that the majority of carcinomata only develop after 25-30 years' exposure ; and a similar long latent period seems to be the rule in all forms of irritation. Cases have been recorded, however, where a malignant growth has followed rapidly on a single trauma. It is not difficult, of course, to get a history of injury from any patient suffering from cancer, but cases in which the evidence is unequivocal have been described. I have, for example, seen an undoubted sarcoma which had arisen at the site of, and a few months after, a fracture of the tibia. Bang [2] has published a remarkable case of cancer of the nose which developed in 16 days on a burn caused by hot tar. A similar case occurred in

[1] *Eighth Scientific Report, Imperial Cancer Research Fund*, p. 98.

[2] *Bull. de l'assoc. pour étude du Cancer*, March 1923, p. 184.

the clinic of Dr. E. G. Graham Little, who has very kindly supplied me with the following notes of it :

"A man aged about 45, a boat builder by occupation, came to see me with two raised and ulcerated lesions on his cheek, each about half an inch in diameter, and presenting clinical appearances so like rodent ulcer that a clerk sitting with me produced a text-book from his lap and showed me a picture which the whole class agreed might have been drawn from the patient. But the history he gave me was very significant. This was that six weeks previously he had been coating a boat with hot pitch, and some of the hot pitch had spurted on to his cheek. In the position of the scald resulting from this accident the ulcers had come. On palpation of glands in connection with the ulcers these were found to be notably enlarged. The diagnosis of a malignant carcinoma was consequently made, and ulcers and glands were freely excised. Almost before the healing of the wound had been completed further and larger glandular swellings appeared. These were again freely removed. The man saw me about six months later when he had glandular masses filling the supra clavicular regions, and he was pronounced inoperable. I understand that he died within a year of the initial accident."

G. M. Findlay[1] has reproduced these observations experimentally in the mouse, and S. Dodd[2] reports similar cases in sheep, whose ears, after branding, are dressed with hot tar.

The significance of these cases will be discussed in the section on the experimental investigation of cancer.

THEORIES

A considerable number of hypotheses have been brought forward by different observers, but none are entirely adequate to explain all the phenomena presented by malignant disease, and many of them beg the question, being merely theories as to how, rather than why, the neoplastic change takes place. Nevertheless, a consideration of them is of value since it enables us to survey the work which has been done in the past, and to clear our ideas on the subject.

In the first place, tumours must be either intrinsic or extrinsic in their origin ; that is to say, they must arise, either as the

[1] *Lancet*, 1925, vol. i., p. 714.

[2] *J. Comp. Path. and Therap.*, 1923, vol. xxxvi., p. 232.

result of some variation from the normal in the cell, due to a complete change of state or function, or perhaps to a developmental error, or the cause must be foreign to the body, entering it or influencing it from the outside.

The first view is the one most generally held, and among the principal theories which have been based on this assumption are those of :

1. Alteration of tissue tension.
2. Embryonic " Rests."
3. Growth liberation.
4. Habit of growth.
5. The biological or reproductive theory.

The upholders of the extrinsic view have devoted their attention to the demonstration of a causal parasite, but, so far, without success.

Intrinsic Theories

1. **Theory of the Alteration of Tissue Tension** (Waldeyer and Thiersch).—It is assumed that a state of equilibrium exists between connective tissue and epithelium, each having an exactly balanced controlling influence over the growth of the other. As the result of their earlier senescence, the connective tissues are supposed to lose this control over the epithelium, which, in consequence, proliferates unchecked. It is further assumed that, once liberated from control, the epithelium is able to proliferate to an unlimited extent.

This theory is inadequate to explain the infiltrative powers of malignant growths or their powers of forming metastases ; it does not take into account the comparative rarity of multiple malignant tumours, and it absolutely fails to account for the occurrence of sarcomata or of the innocent connective tissue tumours.

2. **Theory of Embryonic Rests.**—According to this theory —first enunciated by Durante in 1874 and warmly upheld by Cohnheim—all tumours are supposed to arise in " Rests," or groups of embryonic cells which have become arrested in their development during fœtal life and have taken no part in the formation of the adult tissues. Such " rests " may remain embedded in the tissue or organ they were intended to form, or may be transplanted to different parts of the body ; they are capable of retaining their vitality and powers of growth, and,

in response to some stimulus, irritation, or what not, of undergoing proliferation, forming the neoplasm.

A wealth of evidence has been adduced in support of this doctrine. Roux, in demonstrating the occurrence of fœtal rests in the embryo of the frog, demolished the doubts that were cast upon the existence of such hypothetical aberrant germs; and in man, nodules of tissue closely resembling the cortex of the adult suprarenal gland in their structure may often be found on the surface of the kidney, and, more rarely, on the liver, in the broad ligament, and in the spermatic cord. The frequency of malignant tumours at the orifices of the body, where such developmental errors might be expected to occur, the teratomata and the dermoid tumours, and the malignant transformation of maternal naevi, are all points in favour of the hypothesis.

Yet, although a large number of neoplasms are certainly fœtal in nature, this conception does not apply to all, and it will not explain the definite age incidence of carcinoma, or the formation of malignant tumours in response to irritation in varied situations where there is no evidence of any such congenital derangement.

Even if this theory be accepted, no explanation is forthcoming as to why such "rests" should suddenly begin to grow after having remained latent for so many years.

3. **Theory of Growth Liberation** (Ribbert).—This theory is practically a combination of the preceding ones. Like Cohnheim, Ribbert would ascribe the origin of tumours to "rests," but he claims that these may be "post-natal" as well as fœtal. As the result of long-continued chronic inflammation, he believes that groups of cells are cut off from their normal relationships and become embedded in a strange environment, free from all physiological control, and at liberty to proliferate at will.

So, in carcinoma of the tongue, for example, it is the chronic subepithelial reaction which is primary; the tumour growth from a group of epithelial cells that has been displaced and cut off from the surrounding epithelium by the connective tissue changes, is secondary.

Ribbert and his followers have studied in great detail the histological changes seen in chronic dermatitis and similar processes, and describe a definite "pre-cancerous stage" in these forms of inflammation, but their interpretation of these conditions is not accepted by all authorities. The difficulties in the

way of determining the stage when epithelium is about to become malignant are, of course, quite obvious, and often the inflammatory changes in the connective tissue appear to be secondary to the tumour rather than the cause of it.

Conditions favourable to the production of malignant tumours, according to this conception, exist as a rule in the healing of wounds, yet tumour formation in these cases is the exception. Again, the limitations of growth seen in the transplantation of normal tissue grafts is inconsistent with the theory. Finally, this explanation is adequate only for the carcinomata, and does not apply to the sarcomata.

4. **Habit of Growth Theory**.—Reference has already been made to the anaplastic character of new growths, to the lack of differentiation and reversion to embryonic type exhibited by their cells. This property is such a striking feature of tumours, especially in those of the malignant type, that it has been the subject of much study and speculation, and attempts have been made to elucidate the etiology of cancer by defining the cause of the anaplasia.

Working on these lines, Adami has elaborated his theory of the Habit of Growth.

He holds, in the first place, that the metabolism of the cell is controlled by the nucleus which plays the predominant part, not only in proliferation, but also in the performance of function ; and that in the fully differentiated cell, under normal conditions, practically all the available energy is used up for the purpose of work, leaving little or none for proliferation or growth. The two processes are absolutely antagonistic to one another, and it is only in the undifferentiated cell, or in the fully-developed cell which has undergone retrogression, that growth takes precedence of function. He also points out that, by virtue of inertia, the adult cell tends to maintain its state of functional activity and shows little proliferative power. If, however, as the result of some external influence it is forced to undergo frequent divisions then, because of the same inertia, it will continue to divide and will lose its habit of work.

Adami, then, would regard tumour formation as being in the nature of a reaction on the part of the cell to some external influence acting upon its normal metabolic processes. Either as the result of long-continued cell destruction, or from an alteration in the character of the food supplied to the tissues,

growth gradually supersedes functional activity until it becomes the dominating feature. This theory opens up many possibilities, but it fails to solve the essential question. Chronic irritation and destruction may exist for years without inducing the habit of growth in the cell, though the tissues must be in a state of constant reproduction ; and we have no indication as to why this vital change should occur.

5. **Biological or Reproductive Theory**.—This theory, associated with the names of Farmer, Moore, and Walker, depends upon the recognition in malignant growths of mitoses of the reproductive type (heterotype mitoses). Mitosis, or indirect cell division, is of two types according to whether the cell is destined to form part of the body tissue, or whether it is to become a reproductive element.

In the division of the somatic, or body cells, the chromosomes have a V-shape, and are arranged at right angles to the spindle, splitting longitudinally. In the heterotype mitosis which occurs in the reproductive cells the chromosomes are thicker, have a ring or loop form, and split transversely, being arranged longitudinally in the spindle. Further, in the heterotypical mitosis the number of chromosomes is half that found in the somatic type, in order to allow of the restoration to the normal number after conjugation has occurred between the male and female elements. Professor Farmer and his colleagues have observed such heterotypical mitoses in many forms of malignant growths, and regard the malignant process as being due to a conversion of somatic cells into the reproductive type. Other observers, however, have not been able to confirm these findings, and it should also be noted that the theory can only apply to malignant growths, since in innocent tumours the somatic type of mitosis always obtains.

Extrinsic Theory

Since the earliest times cancer has been looked upon as being of the nature of a parasitic disease. Now, biologically, all tumours are parasites on the organism bearing them, since they live at the expense of the host with an absolute lack of regard for its physiological needs. But it is not in this more general sense that the term is used, for there is a widespread belief in the infectivity of malignant disease.

It is obvious that a certain resemblance exists between a

known infectious disease, such a tuberculosis, and a malignant new growth ; but, as I have already said, the processes are essentially different, and there is no true analogy between the two cases.

A somewhat stronger argument may be advanced in the coccidial disease of the rabbit. Rabbits are frequently found to harbour a protozoon, the coccidium oviforme, which affects especially the liver. Here it is found in the bile ducts, lying free in the lumen or embedded in the epithelial cells. The ducts become greatly dilated, the epithelium proliferates and projects inwards in a papillomatous fashion, and, in the older foci, there is a considerable amount of overgrowth of the surrounding fibrous tissue resulting in the formation of a definite capsule, the whole nodule having the appearance of a papilliferous cyst-adenoma. Here, however, the likeness to true tumour formation ceases ; the process is really more in the nature of a catarrhal inflammation, the epithelium proliferating in response to a definite irritation, and never assuming neoplastic characters.

A certain amount of evidence in favour of an extrinsic cause is afforded by the local incidence of cancer and the reputed existence of cancer houses. It cannot be said, however, that the influence of locality as a determining factor in the production of malignant disease has definitely been proved. Similar physical surroundings are by no means always associated with a high or a low cancer death-rate ; and the available statistics are not sufficiently numerous to put the errors due to chance or co-incidence, or to the confusion of various factors, out of court.

In the literature of a few years ago many examples are recorded of the supposed transference of the disease from one person to another. The infection has been ascribed to actual contact with the individual, as in the case of a healthy person nursing a cancerous patient through a prolonged illness, or is said to have been spread by means of utensils, such as drinking-vessels, or soiled dressings and clothing. But comparatively few of these cases will bear examination. In many of them the evidence is incomplete, and rests entirely upon clinical observation, and in all of them the same fallacies are apparent as we noticed in the statistics of cancer houses.

Further, in direct contradiction to this doubtful evidence we have the fact that no undue liability to cancer has ever been shown to be present among surgeons, nurses, or pathologists

whose professional duties would expose them constantly to infection.

The demonstration of a micro-organism invariably present in tumours, and capable of reproducing experimentally the histological characters of the growth from which it was derived, would of course have settled the question. And at one time or another almost every variety of micro-organism has been associated with the etiology of neoplasms. Micrococci, bacilli, blastomycetes and protozoa, all have had their advocates, but none has stood the test of criticism. Indeed, rather has the variety of the parasites tended to increase the scepticism of the opponents of this theory. The one which has given rise to greater controversy, perhaps, than any other is the Micrococcus neoformans, a coccus closely allied to the Staphylococcus albus, described by Doyen as occurring in non-ulcerated tumours and as being capable of giving rise to true neoplasms on inoculation into animals. But more extended investigations have shown that many non-ulcerated tumours are quite sterile, and even when bacteria can be cultivated from them, in only a certain proportion of cases does the organism bear any relation to the Micrococcus neoformans. And no other observer has been able to produce more than simple granulomata in animals by the inoculation of pure cultures of the coccus. The same criticisms apply to the other parasites mentioned above: the impossiblity of demonstrating their presence in tumours except occasionally, and the failure to produce with them experimentally anything resembling a true neoplasm.

A careful histological examination of carcinomata will often reveal the presence of small extra- or intra-cellular bodies of a definite form, and with different staining reactions from the cells of the tumour. An extracellular form consisting of round bodies, often arranged in groups, and staining deeply with fuchsin, was described by Russell, who regarded them as being blastomycetes. Other observers have found somewhat similar intracellular bodies, situated in the cytoplasm, and sometimes compressing or displacing the nucleus, and these have been looked upon as forms of an intracellular protozoon. These bodies, however, are not peculiar to neoplasms, but may be found in inflammatory conditions, and it is now generally accepted that they are degeneration products occurring in the cell, or nuclear extrusions into the cytoplasm.

The actual demonstration of the cancer parasite, then, has still to be achieved, and there is very little indirect evidence in favour of such an organism.

The experimental propagation of tumours has established the fact that malignant growths can only be transferred from animal to animal by the intact cancer cell; under no circumstances can a dead cell, or the products of cells, give rise to tumours. This statement may possibly require modification in the case of certain sarcomata, but it holds good for all the carcinomata. It is within the bounds of possibility that the initiation of the malignant process may be due to the action of a parasite, but once the cells have acquired neoplastic characters the presence of an organism becomes unnecessary, and all the positive evidence is opposed to it.

Certain metazoa are undoubtedly associated with the etiology of tumours, but their influence appears to be an irritative one only, and not at all analogous to the action of such an organism as the tubercle bacillus. Again, under some conditions, bacteria may stimulate cells to proliferate instead of producing tissue destruction, but we know of no parasite which can confer the power of unlimited growth on any type of cell.

Although, since the question is still an open one, we cannot unhesitatingly deny the existence of an extrinsic cause in cancer, yet we cannot look upon the disease as being a parasitic one in the ordinary meaning of the term, and we must regard the hypothetical cancer parasite as differing essentially from any other pathogenic organism with which we are acquainted.

THE EXPERIMENTAL STUDY OF CANCER

It is only within recent years, since the beginning of the present century, that the study of tumours in the lower animals has been undertaken systematically, but it has already produced a formidable literature. In the space at our disposal it is impossible to do justice to the mass of material which has accumulated during the last decade; one can do little more than indicate the lines along which investigations have been carried out, and the most notable results so far achieved.[1]

[1] The scientific reports of the Imperial Cancer Research Fund are the classical text-books on this subject, and the student is advised also to consult the review by W. H. Woglom, *The Study of Experimental Cancer*, Columbia University Press, 1913.

Although prior to 1903 tumours as they occur in the human being had long been the subject of study, and attempts had even been made to transmit them from one individual to another, but little attention had been paid to neoplasms in the lower animals. Their occurrence was quite well recognised, and, in isolated cases, propagation by transplantation had been carried out with success through several generations of animals of the same species; but the meaning of these observations escaped notice, and it was not until Jensen reported that he had been able to propagate a mammary tumour of the mouse for two and a half years through nineteen generations, that the importance of the study of experimental cancer was fully realised.

Every one whose experience has been limited to the investigation of human material must have felt dissatisfaction at one time or another with the inconclusiveness of his observations. Too often the nature of a tumour is a matter of mere speculation; we see it in only a single phase of its growth, and have no means of judging of its previous behaviour, or of its future possibilities.

In many cases we can fill the gaps in our knowledge of the life-history of a particular tumour from a series of observations of similar growths, but sooner or later a time comes when, in default of facts, we have to fall back upon theories.

The value of working with a tumour which can be propagated in animals through many generations immediately becomes apparent; we can alter at will the conditions under which it is growing, and we can submit it to examination at any period of its growth. Further, it is only under experimental conditions that we can separate essentials from non-essentials, and thereby define the various factors which may predispose to the formation of tumours; while the importance of this method of research in the study of the efficacy and mode of action of palliative and curative measures is obvious.

The vast amount of research which has been carried out along these lines has had important results; and though there has been scarcely sufficient time for them to have influenced current teaching in many particulars, there can be no doubt that our ideas on the subject of tumour formation are being profoundly altered.

By prolonged and systematic investigation it has been shown that innocent and malignant tumours occur in the same variety and situations in mammals, birds, fishes, and amphibians as in

human beings. This is true of both wild and domestic animals, though the latter, of course, offer greater facilities for examination, and supply the greater part of the material. The natural advantages of the mouse as an experimental animal, its small size, its cheapness, and the ease with which it can be handled, have been taken full advantage of, and its neoplasms have been studied in greater detail than those of any other creature; but it must not be forgotten that cancer is ubiquitous in the animal kindgom.

At first these observations naturally met with much adverse criticism, for they strike at the roots of many cherished beliefs as to the influence of such factors as civilisation, diet, environment, and occupation in the etiology of neoplasms in general and cancer in particuler. It became necessary, therefore, to demonstrate beyond all possible doubt the essential similarity between the tumours of mankind and those of the lower animals. One by one the criteria by which we recognise a malignant tumour in the human being were proved to hold good in the mouse and other animals, and the way was cleared for systematic experimental investigation.

Transplantation is effected by inoculating portions of the spontaneous tumour into other animals of the same species; usually the graft is deposited in the subcutaneous tissues, and for routine work the axilla is the favourite site, but inoculations into muscles, blood vessels, viscera, or the peritoneal cavity are equally successful. The graft may be in the form of an emulsion made by mincing the tumour or by cutting it repeatedly with sharp scissors; or small intact fragments may be used, and these give rather better results. Solid fragments are conveniently introduced in a hollow needle of wide bore, fitted with a plunger of such a size that when it is withdrawn a little way it creates a partial vacuum, sufficient to aspirate the graft into the lumen of the needle. For the emulsion, an all-glass syringe graduated in fractions of a cubic centimetre and fitted with a fairly wide bore needle provides a means of delivering with ease an accurate dose.

It is usual to insert the needle under the skin of the groin, and to push it up through the subcutaneous tissues to the axilla before pressing home the plunger. Of course, strict asepsis must be observed throughout the operation.

Should the graft be successful, a tumour which grows progressively develops at the site of inoculation after about ten to

fourteen days. Sometimes the introduced cells remain latent for a much longer period, and it may be several months before an appreciable tumour forms.

The transplanted tumour behaves in every way like a spontaneous growth; it infiltrates the body wall, gives rise to lymphatic and vascular metastases, and eventually causes the death of the animal. From it secondary inoculations can be carried out into other animals, and in this way it can be propagated from generation to generation for a period whose limits have not yet been determined.

The successful propagation of a tumour depends upon two factors: the cells introduced, and the soil which receives them. In the first place, the cells must be those of a malignant growth. Although the cells of innocent tumours and of normal adult and embryonic tissues may show a transient growth if transplanted into another animal, this soon ceases, and the material introduced becomes absorbed. It is only the malignant cell that is capable of continued and progressive growth.

To obtain successful results, it is necessary to inoculate the living tumour cells. Cells which have been disintegrated by repeated freezing and thawing, or saline extracts of cells, are incapable of giving rise to tumours. The cancer cells are also highly susceptible to adverse influences, and are rendered impotent by the action of moderate heat, by drying, by exposure to radium, and, to a less extent, by the action of various chemical agents. Lastly, the dose administered must be considered, for within certain limits a small dose gives better results than a large one.

Under normal conditions the soil appears to be of secondary importance, but it is necessary to realise that the propagation of a tumour is an exceedingly delicate biological experiment, for the tumour cell possesses nothing like the same hardiness as, for example, the tubercle bacillus. One need scarcely say that the inoculations must be into animals of the same species as the bearer of the spontaneous tumour, and in the light of our modern knowledge of cytotoxins it is easy to understand the failure of attempts to transmit human cancer to animals; but even in animals of the same species, differences of race may exercise a remarkable influence upon the success of the experiment. Thus, a tumour in a German mouse which is readily transplantable into German mice, may show a very indifferent growth in the first generations in English mice, though in succeeding generations

the transmissibility improves until the percentage of successful inoculations in the two strains becomes approximately equal.

The tumour cells usually become accustomed to a strange environment after one or two passages, but the early stages of the propagation are often extremely critical. It is the common practice to excise the tumour under anæsthesia, leaving a small portion behind when the wound is closed, or inoculating a fragment into the sound subcutaneous tissues. This fragment often grows with increased rapidity, and offers more favourable material for further attempts at propagation; but in any case it is necessary to inoculate a large number of animals, for the percentage of successes in the first generation is likely to be small.

I have said that to be viable the tumour cell must be undamaged. This is true of every propagable tumour except the infective sarcoma of the fowl, first described by Peyton Rous, of which some half dozen strains are now in existence. This neoplasm can be propagated, growing with extreme rapidity in later generations; it exhibits infiltrative growth, and forms metastases. The first tumour described by Rous was originally only transmissible to fowls of the same breed as the bird bearing the primary tumour; but now, in common with other strains, it grows in other races. It exhibits, however, this peculiarity: filtered extracts of it, when inoculated into fowls, give rise to tumours indistinguishable in their character and behaviour from the spontaneous growth and the products of ordinary transplantation.

The resemblance between granulomata and sarcomata is of course notorious, and it may be that we are dealing here with an infective process and not a neoplasm. But for a long time all attempts to demonstrate an infecting agent, or virus, were unsuccessful. Recently, however, W. E. Gye[1] has reported its discovery. He finds that a filtered extract of the tumour contains two substances: (1) a particulate, living virus, and (2) a non-particulate thermolabile chemical substance. Neither of these is capable of producing a tumour when injected alone into fowls, though they do so when injected together. The particulate virus can be cultivated *in vitro*; the accessory chemical substance, derived from the tumour cells, governs infection and carries the specificity which is the most conspicuous feature of the tumour. The conception of the Rous tumour put forward is that

[1] *Lancet*, vol. i., p. 1183, 1925, and private communication.

the virus is the extrinsic cause of the tumour but that it is not specific to the fowl. This has been shown as follows: the virus can be replaced by virus obtained from a rat sarcoma, a rat carcinoma, a mouse carcinoma and a human carcinoma. The combination of any one of these viruses and the chemical factor of the Rous chicken sarcoma will produce a sarcoma in a fowl indistinguishable from the Rous tumour as ordinarily obtained by transplantation of cells. The importance of this work, if it is confirmed, can scarcely be exaggerated from the point of view of general pathology, and in the more limited field of tumour pathology it raises questions of the first moment. Inasmuch as the Rous tumours have all the recognised characters of sarcomata, the parasitic nature of, at any rate, one form of malignant growth would seem to be proved.

It is the practice in research laboratories to preserve graphic records of the progress of transplanted tumours in the form of silhouettes which accurately reproduce their measurements and contours. The animals are examined, and their tumours are charted, at stated intervals, usually once a week, and although an enormous amount of labour is thus entailed, it is the only method by which it is possible to see at a glance the rate of growth and the proportion of "takes" in a batch of inoculations, and which will permit of a rapid comparison with the behaviour of previous generations of the tumour.

These graphic records, however, can only be applied to tumours which have become definitely established, and it is equally vital to know what happens to the graft before it gives rise to a measurable growth. The immediate effects upon the graft of transplantation to a fresh soil have been thoroughly investigated, and the examination of "early stages," as it is called, has resulted in establishing important principles.

The method consists in the inoculation of a batch of mice with small particles of tumour tissue, sacrificing two or three animals at definite intervals, say 6, 12, 18, 24 etc. hours after inoculation, and submitting the graft together with the surrounding tissue to microscopical examination. Surplus animals are allowed to survive, and their tumours are regularly charted, thereby providing a control on the microscopic findings. It is necessary to observe the most rigid asepsis in order to avoid the introduction of any disturbing element along with the graft; and for the same reason the skin must be epilated before it is punctured with the

needle. The whole procedure is extremely laborious, for not only must the various steps in the experiment be carried out with the utmost care, but the grafts themselves must be cut in serial sections, and examined in their entirety.

For a short time after the inoculation no change is visible, but within a few hours there occurs a transient aggregation of leucocytes in the substance and neighbourhood of the graft. This is soon followed by a proliferation of the connective tissue cells in the adjacent areolar tissue, and at the end of twenty-four hours the graft is surrounded by a well-marked zone of fibroblastic reaction. By this time changes also become apparent in the graft itself. The tumour parenchyma remains practically unaltered, but hyaline degeneration can be distinguished already in the supporting stroma. Degeneration of the introduced stroma becomes more and more marked until, at the end of three days, it is extreme. In the meantime the reaction in the surrounding areolar tissue becomes more pronounced, and from the fourth day onwards there is an active replacement of the degenerated stroma by the connective tissue of the host. Fibroblasts pass in from all sides between the groups of tumour cells, accompanied by outgrowths from the capillary vessels, and eventually, by about the twelfth day, the graft is fully vascularised and supplied with a new stroma from the tissues of the host.

This sequence of events, first followed out in detail in the case of Jensen's tumour, has since been shown to obtain with a variety of other tumours, and it may be regarded as established that in the propagation of a malignant new growth it is the parenchyma alone which survives, the introduced stroma being invariably replaced by the tissues of the host. These studies have also shown that the propagated tumour is derived entirely from the parenchyma of the graft, and does not depend in any way upon the initiation of a malignant growth in the corresponding epithelial cells of the host. Finally, it appears that the survival and continued growth of the graft is absolutely dependent upon the provision of a vascularised stroma by the host ; in the absence of this reaction, the tumour parenchyma suffers the same fate as the connective tissue, and the whole graft eventually becomes absorbed.

In any series of inoculations a certain number of mice fail to develop tumours. The number varies within wide limits, and often depends largely upon the technique employed, but,

nevertheless, some animals possess naturally a relative resistance to inoculation compared with their fellows. This resistance may be racial in character, and English mice may differ from continental animals in their behaviour to a given tumour. Again, young animals are less resistant than old, and therefore provide better subjects for experiment.

It was obviously of immense importance to discover whether this natural resistance could be increased artificially; in other words whether an acquired resistance or immunity could be induced.

It was noticed that in some experiments the inoculated tumours after growing for some time remained stationary, and finally became absorbed. Attempts to reinoculate the animals in which this spontaneous absorption had taken place with the same tumour were unavailing, and they were also more resistant to inoculations with other tumours than normal mice. The absorption of a growing tumour, therefore, induces a power of resistance in the mouse which is absolute in respect to the original tumour, and relative in respect to other growths.

A similar immunity is induced in mice by the unsuccessful inoculation of a tumour graft, but only when the cells introduced are healthy; a disintegrated or dead cell can no more render an animal resistant than it can give rise to a tumour.

A great step in advance was made when it was found to be possible to produce immunity by the inoculation of normal tissues. It was shown that an inoculation with defibrinated mouse blood was capable of giving rise to a refractory condition in mice, and a futher analysis of the experiment made it clear that the corpuscles, not the serum, were the essential factors in the process.

Emulsions of normal organs, of complete embryos, and of embryo skin were found to be equally effective, but it must be clearly understood that in each case the reaction is quite specific; a mouse can be rendered resistant only by inoculation with mouse tissue, and a rat with rat tissue.

The induced resistance reaches its height in about ten days and lasts about as many weeks, though towards the end of that time it becomes very feeble.

It is possible, then, to render normal animals resistant to inoculations with tumour tissue; but the greater problem is still to be solved, and we are unable to influence a growing tumour by these methods.

Attempts to confer passive immunity have also failed, and there is no evidence that the blood of resistant animals is capable of conferring a higher degree of immunity than the blood of normal animals.

The nature of the resistant state is still the subject of controversy, and it would serve no useful purpose to enter upon theoretical discussions ; but the effect upon the refractory animal has been clearly worked out. A resistant animal differs from a normal one in that it fails to provide a stroma for the tumour graft ; but the explanation of this inactivity is as yet undetermined.

To the student of human pathology some of the most interesting phenomena encountered in the propagation of tumours through many generations relate to variations occuring in their histological structure. In the study of human material our investigations are limited to a comparatively brief period in the life history of the tumour ; but in experimental cancer there is no such restriction, and it is possible to keep a tumour under observation for many years.

A number of propagable tumours retain their histological characters and transplantability unchanged through many generations ; others show during propagation profound alterations in their structure and biological behaviour. The whole question is one of great complexity, but it is permissible to single out a few of the salient features, since they are of special significance to the general pathologist.

In an ordinary carcinoma of the human breast it is common to find acinous areas mingled with solid alveoli, and a similar structure may obtain in corresponding tumours of the mouse. In the course of propagation these tumours may exhibit from time to time stages in which the alveolar or the acinous structure becomes more prominent, though there is never any doubt as to the identity of the transplanted with the primary growth. In other cases, however, the histological structure may undergo a permanent change, and acini may be replaced entirely by solid alveoli.

Other instances have been observed in which a mixed alveolar and acinous structure is combined with areas in which the epithelial cells are so altered as to be almost identical in appearance with those of a spindle-celled sarcoma, but in subsequent generations the sarcomatous-looking cells revert back to the epithelial type.

Even more remarkable are those keratinising tumours which

present at one and the same time areas having the typical structure of a squamous-celled carcinoma with prickle cells and keratinisation, along with others having the usual acinous or alveolar histology. The connection between the three types of growth is so intimate that differentiation into squamous cells with keratinisation may appear in one part of a single acinus. After some time the squamous-cell differentiation may be lost, but for several generations the variations in the histological structure may be very pronounced.

The recognition that the tumour cell possesses such possibilities in the way of polymorphism should go far to explain some of the anomalous neoplasms met with in human pathology, and should tend to make us somewhat cautious in their interpretation. A broad outlook is essential in so intricate a subject, and if this appears to engender an attitude of undue agnosticism, this is at least a fault on the right side.

In a rather different category are those cases in which the stroma of the growth ceases to play a subsidiary part. Several cases have now been recorded where, in the propagation of a mammary carcinoma, an unusual activity became apparent in the stroma of the growth, eventually resulting in the development of a definite sarcoma. Once the sarcomatous change appears, it rapidly gains the ascendency and completely replaces the carcinomatous element. By appropriate measures it is possible to propagate both strains simultaneously, or to separate one from the other ; and experiments seem to show that the age of the carcinoma is the determining factor in inducing the change in the connective tissue.

The condition has also been found in spontaneous tumours of the mouse, though propagation in these cases resulted in the growth of a pure sarcoma alone.

So far, the reverse process has not been demonstrated, and no propagable carcinoma has arisen in the transplantation of sarcomatous tissue in the neighbourhood of epithelial organs.

The study of the transplanted tumour has yielded results of the first importance and has taught us more about the nature of cancer than we could possibly have learnt in any other way. But it has its limitations, chief of which is that it tells us little or nothing about the initiation of the malignant process. Before we can hope to increase our knowledge in this direction it is necessary that we should be able to produce tumours in experi-

mental animals. For a long time all attempts to do this were unsuccessful. It is true that sarcomata have developed during the propagation of transplantable carcinomata. Again, Fibiger has shown that cancer of the stomach and mouth can be brought about in rats by feeding them with a nematode, *Gongylonema neoplasticum*. And Bullock and Curtis have caused sarcomata of the liver, also in rats, by feeding these animals with the ova of *Taenia crassicollis*, the sarcomata developing in the inflammatory tissue surrounding the larvæ (*Cysticercus fasciolaris*). But for the induced tumour to be of any value for experimental purposes it must be possible to produce it with regularity; moreover, the tumour must be superficial so that its development and growth may be studied with ease, conditions which are not fulfilled by any of the tumours mentioned above. Yamagiwa, Ichikawa, and Tsutsui have, however, begun a new chapter in Cancer Research by demonstrating the possibility of producing carcinomata of the skin of rabbits and mice by the repeated applications of tar. Their observations have been actively followed up by other workers and important results have already been obtained.[1]

The technique adopted is briefly as follows: mice are the animals of choice; rabbits are not very suitable, and guinea pigs and rats are definitely refractory, though sarcomata can be produced in rats by repeated subcutaneous injections of tar, a point of some interest since connective tissue tumours are normally more common in these animals than carcinomata.

The skin of the back between the shoulders is epilated, and the bare area is painted with ordinary gas tar, usually twice a week. Various extracts of tar, as well as crude paraffin oil and arsenious acid, have all been used successfully, but gas tar serves the purpose perfectly well. Prolonged tarring is necessary, for although tumours develop in some mice in from 3 to 4 months, in the majority of animals 6 to 9 months is necessary, and some animals have proved refractory after 18 months' treatment. The tarring need not be continuous, for if it be discontinued after 3 to 4 months the tumours develop in the ordinary way. By combining scarification of the skin with tarring, Deelman has reduced the latent period to a quarter of the normal time or even less; and G. M. Findlay has obtained much the same result by

[1] See *Seventh and Eighth Scientific Reports of the Imperial Cancer Research Fund*, where the literature is referred to.

combining tarring with exposure to ultra-violet light. At the same time, there appears to be an upper limit beyond which irritation is ineffectual in producing cancer. Just as inadequate stimulation is not followed by a malignant growth, so excessive irritation may fail to cause the proliferative process. From the clinical and experimental observations of the production of cancer by a single trauma (p. 39), it would seem that repeated injuries are only necessary because we do not know exactly the changes which occur in the development of the malignant cell. A closer analysis of the process should enable us to define accurately the nature and degree of the requisite stimulus. Experiments of even greater significance have been reported by Murray, who has found that mice in which tumours have developed spontaneously or as the result of the application of tar become refractory; tarring of such animals is not followed by tumour growth. These observations, which, of course, are in agreement with the comparative rarity of multiple malignant growths in man and animals generally, suggest that although cancer is a local process, a profound systemic change accompanies its development. The likelihood of this is enhanced by further experiments. If mice are tarred simultaneously in two separate places two tumours develop much about the same time. If, however, tar is applied to one site some weeks before the other, the tumours again appear more or less simultaneously. In other words, the latent period for the second tumour is cut down; instead of being rendered refractory by the preliminary treatment, which, it must be understood, has not yet resulted in the production of a tumour, the animal is made more susceptible.

This work is so recent, and so much of it is still in the making, that it is scarcely possible to appraise its value. Nevertheless, it would seem to have important application to human pathology. It explains the age incidence of cancer, for it shows that chronic irritation is only followed by tumour growth after a long latent period; and it gives a reason for the rarity of multiple tumours. And while it forces us to entertain the uncomfortable possibility that the cancer of middle age may be due to some factor which may have ceased to act for many years, it suggests the presence of a systemic change in cancer which may prove of importance in diagnosis or even prophylaxis.

Another line of investigation which has produced equally striking results is that of tissue culture. The cultivation of tissues

in vitro is a valuable method for the study of the growth and survival of cells and, especially, of the effects upon them of various substances which may be added to the nutrient medium. Working with a saline medium enriched with an extract of embryonic cells, Drew has obtained results of great interest. He finds that embryonic, adult and tumour cells all grow in this medium, but whereas embryonic and tumour tissues proliferate almost immediately after implantation, adult tissues do so only after a lag of some ten days. This lag may be abolished by the addition to the medium of a saline extract of normal adult tissue which has been disintegrated and incubated at body temperature. The destruction of normal tissue, therefore, produces a substance which is capable of stimulating growth in normal tissues. The healing of wounds has long been thought to be due to the presence of substances of this nature, and their existence is now definitely proved. Extending this line of enquiry, Drew has shown that a similar growth-stimulating substance is present in saline extracts of *non-autolysed* malignant cells; that is to say, tumour cells possess already formed an activating substance which can only be got from the normal cell by the degradation of its protoplasm.

These observations suggest that the malignant cell differs from the normal because it has acquired a new property. The continued growth of a tumour is not due to its liberation from inhibitory influences, tissue tension and the like, but is the manifestation of a new power which its cells have developed. This conception brings the malignant tumours into line with benign growths, processes of repair and hypertrophy and so forth. It offers an explanation of the experimental results of Deelman already quoted, and of many other facts of human and experimental pathology; and it is possible that it may be a means of enabling us to distinguish between true neoplasms and blastomatoid processes.

That the malignant cell differs metabolically from the normal cell in other respects has also been shown by *in vitro* experiments. In cultures of normal tissues the difficulty lies in the initiation of the growth; once this is established continued propagation is fairly easy. Tumours, on the other hand, grow much more readily in culture media, but they die quickly unless frequently subcultured. This is because they elaborate during growth metabolic products which are highly toxic; growth can only

be maintained if these are constantly removed by changing the medium. Such toxic substances are not produced to anything like the same degree by normal tissues, and have apparently no deleterious action on cultures of normal tissues.

A more exact determination of these metabolic differences has been attempted by Russell, who has shown that slight but constant differences exist between normal and cancerous tissues in their action on various sugars outside the body. Whether or not the study of the cancerous tissues along these lines will reveal such modifications of metabolism in the malignant cell as to make a therapeutic attack upon it possible, remains to be seen; but the results so far obtained suggest interesting possibilities.

TREATMENT

The treatment of malignant disease is one of the most urgent and difficult problems with which medical science is confronted, and it can scarcely be claimed that laboratory studies have as yet afforded the clinician much active assistance. Nevertheless, a few broad principles have become more clearly defined, and it may be useful to devote a short space to their consideration.

In the first place, all the known facts go to show that "cancer" is a purely local condition, and not a particular manifestation of a general disease; complete extirpation of the tumour will result, therefore, in a permanent cure. The limited success of operative treatment in no way negatives this statement, for recurrences are due to *incomplete* removal of the growth. Similarly, the occurrence of multiple tumours must be regarded as a coincidence, and not necessarily as indicating a constitutional tendency to the development of cancer.

On the other hand, we know of no agent which has a specific destructive action on the malignant cell, for careful investigation has always failed to substantiate the claims brought forward from time to time in support of the various "cancer cures." Nevertheless, the possibility of a successful treatment for cancer must not be lost sight of, for there are in the literature several authentic examples of the spontaneous cure of malignant growths. Rohdenburg [1] in a review of the subject points out that since spontaneous regression of tumours does sometimes occur it should

[1] G. L. Rohdenburg, *Journal of Cancer Research*, vol. 3, No. 2, p. 193.

be possible to bring it about at will. It is known that tumours constantly vary in their growth energy, and if the factors controlling this variation could be discovered, there is no reason why they themselves should not be controlled. But for the present, and for some time to come, surgery is, and must be, of paramount importance in the treatment of the disease.

The removal of an innocent tumour is merely a matter of surgical technique, though it may be contra-indicated from anatomical or physiological considerations, but the infiltrative growth and powers of dissemination of the malignant neoplasm make its ablation a much more serious procedure. It is necessary to remove not only the tumour itself and any obvious secondary deposits, but also those tissues which are most likely to have become invaded ; at the same time it is not justifiable to expose the patient to an unduly severe operation.

These two conditions can only be fulfilled if the surgeon is aware of the general mode of spread of malignant growths, and the particular paths of invasion in the different parts of the body.

Modern pathological research has placed the operation for the removal of the cancerous breast upon a scientific basis, but much work remains to be done in respect to paths of spread in other organs.

But even the most carefully planned attempt at complete eradication is unavailing in the presence of the more widespread dissemination which occurs in the older and more rapidly growing tumours. It is obvious, then, that the earlier a malignant tumour is diagnosed, the better is the prospect of a surgical cure, for there is less chance of dissemination having taken place.

Now, early diagnosis can only be secured by the active co-operation of the patient, and it is of the utmost importance that the public should be warned of the dangers of delay, and urged to obtain a medical opinion on every indolent ulcer or tumour, however small. In the case of uterine carcinomata some educational measures have already been adopted, but the significance of untimely or excessive vaginal hæmorrhages is still far from being recognised.

It frequently happens that the surgeon is uncertain as to the malignancy of a tumour, and in doubt as to whether he should perform the major operation or be content with a local excision. His doubts may often be set at rest by a simple incision and inspection of the tumour ; but a naked-eye examination is

notoriously unreliable, and he may require the assistance of the microscope.

Two courses are then open to him : he may remove a portion of the tumour, or the whole of it, submit it to the pathologist for examination, and complete his operation at a later date if the report indicates the necessity for further measures ; or he may requisition the immediate co-operation of the pathologist in making a microscopic examination on the spot.

The first course is open to criticism in that the patient may be called upon to undergo two operations where one should have sufficed. Another objection is that the preliminary incision may result in opening up vascular and lymphatic spaces, with a consequent likelihood of the dissemination of the growth during the time that must elapse before the second operation.

In many respects it would seem to be more satisfactory to arrange for a microscopical examination during the operation, but this method of the " rapid diagnosis " also has its disadvantages.

With the modern carbon dioxide freezing microtome sections of fresh material can be prepared in less than five minutes, but no adequate fixation can be attempted, and the tissue will necessarily be very distorted. The pathologist must rely, therefore, on a hasty examination of a very indifferent section.

Further, there is no guarantee that the really suspicious area is being examined ; the preliminary investigation is scarcely likely to be very thorough, and a small cancer may well be overlooked. In early carcinoma of the breast, for instance, the small malignant area may be so overshadowed by mastitis or a simple adenoma as to escape notice. So, should the pathologist report the growth to be innocent, all the surgeon knows is that that particular part is innocent ; he is still in ignorance as to the condition of the rest of the breast.

But perhaps the greatest objection is that it may be impossible to give a definite pathological diagnosis of the innocency or malignancy of a tumour, especially from the examination of a single section. A tentative opinion is all that can be expressed, and different pathologists may vary in their interpretation of the same section. This is frequently the case in frozen work. The typical carcinomata and well-marked inflammatory lesions offer few difficulties, but the more atypical carcinomata and all sarcomata may easily defeat the most confident histologist.

It is in the difficult borderland cases that the aid of the rapid histological examination is most frequently sought, since the surgeon who consistently follows his tumours to the laboratory is familiar with the naked-eye appearances of the more typical growths, and it is in just this class of case that a careful consideration of good preparations is most needed.

Lastly, the pathologist knows that the only cure for cancer is early and wide excision. Working under grave disadvantages, and fearful lest undue importance should be attached to his opinion, he is likely to be biased in favour of diagnosing malignant disease, thus possibly exposing the patient to an unnecessarily severe operation, and so defeating the very object for which he was called into consultation.

A technical detail of very great importance is concerned with the readiness with which malignant cells may be transplanted into the healthy tissues of the person bearing the tumour. Clinically, the process is well recognised (p. 24), and experimental research has demonstrated the ease with which autoplastic inoculations can be carried out. It is therefore very necessary to discard immediately any instrument which may have come into contact with malignant cells during the course of the operation.

Under certain circumstances it may be more desirable to attempt the destruction of a neoplasm *in situ*, rather than to remove it by a surgical operation. This applies especially to superficial neoplasms of a low grade of malignancy, such as rodent ulcers of the face, where a wide excision would leave an unsightly scar. Various caustic substances were formerly utilised for this purpose, but they are now entirely replaced by applications of X-rays, radium, or carbon dioxide snow, or by ionisation.

This form of treatment is still in the experimental stage, and it may seem scarcely permissible to discuss it in a pathological treatise, for, in the absence of a sufficient number of controlled laboratory observations, only a wide clinical experience can warrant an opinion on the relative or absolute merits of the different agents concerned. Our knowledge of the action of radium on the malignant cell, for example, is still far from conplete. There is no doubt that it causes extensive destruction in a tumour, but there is no absolute evidence that it exercises a greater effect on malignant than on innocent tissues. A microscopical examination of a tumour after it has been exposed to

radium reveals a considerable degree of destruction of the tumour parenchyma, together with an active proliferation of the supporting stroma. Even in the degenerated areas, however, healthy parenchyma cells can be distinguished, and the radiations have little effect on the deeper parts of the growth.

Patients in whom superficial tumours have been successfully treated by local applications of various kinds seldom come to the notice of the pathologist, but from time to time he becomes aware of the failures. It may be, therefore, that he is not in a position to express a sound opinion on this method of treatment. Nevertheless it is only right to say that I have seen the most disastrous results follow the application of these different agents, and I am strongly of the opinion that superficial tumours, whether diagnosed as rodents, naevi, or what not, should always be treated by excision unless there are the strongest reasons against an operation.

The palliative treatment of inoperable malignant disease scarcely comes within our province, though it may tax the resources of the physician to the utmost.

Applications of X-rays or radium may be employed to relieve local symptoms, while the evil effects of bacterial invasion of the tumour may be combated by vaccines.

The vaccine most frequently employed is one prepared from a culture of the Micrococcus neoformans, but it is well to realise that this organism is by no means invariably present in tumours, for staphylococci, streptococci, or other microbes may be the infecting agents.

Coley's fluid, a preparation of the toxins of streptococci and B. prodigiosus, has been used with some success in the treatment of sarcomata. The treatment is based on the observation that sarcomata may retrogress, or even disappear entirely, after an attack of erysipelas.

Lastly, one may point out that in some cases a local removal of a malignant tumour may be quite justified, although no hope exists of a permanent cure. A complete excision of a cancerous tongue, for example, or of a fungating tumour of the breast, even though there be distinct generalisation of the growth, may relieve symptoms very considerably, and do much to mitigate the patient's lot.

PART II

THE GENERAL PATHOLOGY OF TUMOURS

TERMINOLOGY AND CLASSIFICATION

The terminology adopted in the study of tumours is in a considerable degree of confusion. The term Tumour applies to any swelling, and although among pathologists it has a more restricted meaning, clinicians still employ it, and quite justifiably, in its older sense, and apply it to inflammatory swellings, collections of fluid, and simple hypertrophies as well as to true autonomous tumours.

We are therefore in need of a more distinctive term. "Neoplasm," and its English equivalent, "new growth," are somewhat cumbersome, and although their application is more limited by convention, they are still used in connection with other varieties of tissue production. Teratoma and Blastoma are gradually gaining acceptance, but it is doubtful if the custom of years will ever be broken down, and the various terms are used indiscriminately.

A Teratoma is a tumour derived from totipotential cells, that is to say, cells capable of giving rise to all the tissues of the body. It may be heterochthonous, derived from another individual, or autochthonous, derived from the same individual.

A Blastoma is a tumour arising from unipotential cells, cells capable of forming only one variety of tissue. Blastomata are, for the most part, autochthonous, but one form, the Chorion-epithelioma, is heterochthonous, since it is derived from fœtal or foreign cells.

The majority of innocent tumours are named from their constituent tissue, the termination *oma* being added; and custom has sanctioned the use of both the classical and the English forms

of the plural, so that it is equally correct to speak of fibromas and fibromata.

The malignant epithelial tumours are classed together as Carcinomata, and, similarly, the malignant connective tissue tumours are called Sarcomata.

The terms ***Typical*** and ***Atypical*** demand some explanation. By some authors they are used to express innocency and malignancy. Thus, a tumour composed of fibrous tissue may be either innocent or malignant, a fibroma or a fibrosarcoma. In the former case its structure closely resembles that of normal fibrous tissue, and it is said to be ***typical***; in the latter, the structure of the tumour and its constituent cells show marked variations from normal fibrous tissue, differences which are reflected in its mode of growth, and in consequence it is described as being ***atypical***. By others the words are used to qualify a tumour, not with reference to the normal tissues, but to other forms of the same class of growth. So we may speak of a typical squamous carcinoma, meaning a malignant growth derived from squamous epithelium, which resembles in its characters the majority of the tumours derived from similar tissues.

Various other terms are in use, but many explain themselves, and we may with advantage leave the consideration of the remainder until the necessity for their use arises.

CLASSIFICATION

So many varieties of tumours exist, and transitional forms are so numerous, that the task of arranging them in an orderly classification is no easy one.

To be of real value such a classification should not only group tumours according to their general structure, but should also indicate their physiological and biological relationships to one another, so that if we are able to place any particular neoplasm in its proper division, we may have some indication, at least, of its biological properties.

Attempts to achieve this ideal have been only moderately successful, for in their mode of growth and clinical behaviour tumours are subject to even more marked variations than they are in their anatomical features.

Any scheme of grouping, therefore, must be of the nature of a compromise if it is to remain of reasonable length.

The subject has been approached from two different points of view, the histological, and the embryological or histogenetic, both of which have their advantages and disadvantages. In the histological classification attention is directed solely to the type of cell or tissue of which the growth is composed, and tumours are arranged according to the corresponding elements from which they arise. In the embryological system the tumours are traced back beyond their corresponding adult tissues, and are grouped according to the varieties of immature or undifferentiated cells which give origin to the fully developed tissues of the body.

Very early in the development of the embryo the individual cells are marked out to form the different organs and tissues of the body, and for this purpose are endowed with certain characteristics. Provided that they remain in their normal relationship to the other cells of the embryo, and are subjected to no adverse influences, they will eventually give rise to structures having definite functions and possessing a constant histological formation. If, therefore, we can with certainty refer a tumour to any particular class of embryological cell, we should be able to hazard an opinion as to its probable behaviour and mode of growth. For this reason the histogenetic classification is, theoretically, the more scientific. In practice it is not so helpful as might be supposed, and, moreover, has to be combined to a greater or less extent with histological systems; nevertheless it opens up many lines of thought, and is undoubtedly conducive to a broader outlook than any purely morphological classification.

But it must not be forgotten that any scheme based upon embryological studies rests to a considerable degree upon a foundation of theory. Until we possess a more exact knowledge of the development of the body, we may come to adopt entirely false conceptions as to the nature of many neoplasms by a too slavish adherence to considerations of cell activity.

Therefore, although a combined morphological and histogenetic classification appears to be the most scientific, it is well to bear in mind also those which depend on morphological characteristics alone.

Of the various histological classifications, possibly the simplest and most satisfactory is that devised by Powell White.[1] Following the lines of his definition of tumours, this author divides them

[1] *The Pathology of Growth*, "Tumours." London, 1913.

into three main classes, Organomata, Histiomata, and Cytomata, according to whether they consist of organs, tissues, or cells; and the second and third groups are subdivided as often as may be necessary in order to permit of distinction between the various types of tissues and cells which may be represented.

Thus, a cyst of the ovary containing skin, hairs, and glands, that is to say, organs or rudiments of organs, would be placed among the organomata; a tumour composed of atypically arranged tissues, epithelial tubules with a supporting stroma but with no definite glandular arrangement, for example, is a histioma; while a tumour made up of cells which form neither organs nor definite tissues is a cytoma.

We have, then, the following Table:

A. Organomata, or Organ Tumours.
   1. Teratoma.

B. Histiomata, or Tissue Tumours.

   (*a*) Desmomata, or supporting Tissue Tumours:
      1. Myxoma arising from mucous tissue.
      2. Fibroma ,, ,, fibrous tissue.
      3. Lipoma ,, ,, fat.
      4. Chondroma ,, ,, cartilage.
      5. Chordoma ,, ,, notochordal tissue.
      6. Osteoma ,, ,, bone.
      7. Odontoma ,, ,, dentine.
      8. Glioma ,, ,, neuroglia.

   (*b*) Neuromata, or Nerve Tumours.
      1. Neuroma arising from nervous tissue.

   (*c*) Myomata, or Muscle Tumours.
      1. Rhabdomyoma arising from striated muscle.
      2. Leiomyoma ,, ,, smooth muscle.

   (*d*) Lymphomata, or Lymphoid Tissue Tumours.
      1. Lymphoma arising from lymphoid tissue.
      2. Myeloma ,, ,, bone marrow.

   (*e*) Epithelial and Endothelial Histiomata.
      1. Papilloma.
      2. Adenoma.
      3. Angeioma.

C. Cytomata, or Cell Tumours.
   (*a*) Blastocytomata arising from indifferent cells.
   (*b*) Sarcomata (desmocytomata) arising from supporting tissue cells.
   (*c*) Neurocytomata arising from nerve cells.
   (*d*) Myocytomata ,, ,, muscle cells.
   (*e*) Lymphocytomata ,, ,, lymphoid cells.
   (*f*) Carcinomata ,, ,, epithelial or endothelial cells.

This Table has certain obvious advantages. It is short and easy to remember. The Histiomata and the Cytomata correspond respectively to the two main groups, the innocent and the malignant, which alone have any real clinical significance. Apart from this, there is certainly nothing in the classification itself to indicate the biological properties of any particular tumour. But these are best learnt by experience ; indeed, only an intimate acquaintance with the subject, the result of years of study, can warrant an authoritative opinion in this respect with regard to a large proportion of individual neoplasms. It has, however, this great disadvantage. It depends for its success on an accurate interpretation of histological appearances, at which it is not always possible to arrive. In the first two groups there is seldom much difficulty in determining the histological structure of the tumour, but with regard to the cytomata it is, in some cases, by no means easy to decide upon the type of cell of which the growth is composed. This is specially noticeable in respect to the hypernephromata, the melanomata, and certain other varieties ; and the necessity for adopting a dogmatic attitude with regard to these in the absence of any exact knowledge as to their nature, constitutes a serious drawback. Moreover, the endotheliomata often differ so widely in their structure from the cytomata derived from epithelial cells, that it is scarcely justifiable to include them both under the heading of Carcinomata.

Turning to the Embryological classifications, we find that the older forms were based on the recognition of three primitive orders of cells forming the epiblast, hypoblast, and mesoblast of the embryo, and three varieties of tumours were described according to their supposed origin from derivatives of one or other of these layers. But very obvious difficulties soon became apparent. For example, many tumours of the central nervous system were placed in the epiblastic group, though they differ widely in their histological features from other tumours of epiblastic origin, resembling more closely the mesoblastic, or connective tissue growths. Again, undoubted glandular tumours are found in the kidney, an organ of mesoblastic origin though having a glandular structure.

Modern research, however, has done much to clear away these anomalies, and, utilising the results of more recent studies, Adami has suggested a classification which has many features to

recommend it. He points out that each of the three primitive layers of the embryo gives rise to two orders of cells, those forming "lining membranes," and those forming solid tissues or "pulps." Thus, not only does the epiblast form the covering epithelium of the body and the structures immediately derived from it, but an ingrowth of it develops into a solid structure, the central nervous system. And the hypoblast gives rise to solid "pulp" tissue in the notochord, as well as the lining membrane of the alimentary canal, and outgrowths from it such as the liver and pancreas.

In the mesoblast, which is composed of cells derived from both epiblastic and hypoblastic layers, a similar differentiation is observed. It divides into two portions: (1) the mesothelium or lining membrane of the primitive body cavity, and (2) the mesenchyme, or body mass. From the mesothelium are developed organs such as the kidney and suprarenals, as well as the lining membranes of the serous cavities, and also solid outgrowths which become the myotomes, giving rise to striated muscle. From the mesenchyme are formed the connective tissues of the body, and also lining membranes, in the endothelium of blood and lymphatic spaces.

Developmentally, then, the cells of the body may be divided into two main types:

(*a*) The "lining membrane," "rind," or "lepidic" cells, and (*b*) the "pulp," or "hylic" cells.

Cells of lepidic tissues are in close apposition to one another, and are not separated by any intercellular tissue, their nutrient vessels being contained in a coarse hylic tissue stroma. Cells of hylic tissue, on the other hand, are separated from one another by an intercellular substance, and the nutrient vessels tend to lie in close contact with them.

With this embryological basis Adami divides tumours into two main groups: (1) Lepidomas, arising from lepidic or lining membrane tissues, and (2) Hylomas, arising from hylic or pulp tissues. Further, the Lepidomas are divided into two classes, (*a*) Primary, and (*b*) Secondary, or Transitional, according to whether the cells have descended directly from the original epiblast or hypoblast, or whether they have passed through a mesoblastic stage.

His full classification is as follows :

I. Lepidic, or Rind Tumours.

A. Lepidomas of the First Order.

1. Of Epiblastic Origin.

(*a*) Typical : Papilloma, epidermal adenomata (of sweat, salivary, sebaceous, and mammary glands, etc.).

(*b*) Atypical : Squamous epithelioma, carcinoma of glands of epiblastic origin.

2. Of Hypoblastic Origin.

(*a*) Typical : Adenoma and papilloma of digestive and respiratory tracts, thyroid, pancreas, liver, bladder, etc.

(*b*) Atypical : Carcinoma developing in the same organs and regions.

B. Lepidomas of the Second Order, or Transitional Lepidomas.

3. Of Mesothelial Origin.

(*a*) Typical : Adenoma of kidney, testicle, ovary, urogenital ducts ; adenoma of uterus and prostate ; adenomas originating from the serous membranes, " Mesotheliomas " of pleura, peritoneum, etc.

(*b*) Atypical : Cancer of the above-mentioned organs ; squamous endothelioma, so called, of serous surfaces, epithelioma of vagina ; adrenal mesotheliomas, hypernephroma.

4. Endothelial Lepidomas.

Tumours originating from the endothelium of the blood and lymph vessels ; lymphangeio-endothelioma, hæmangeio-endothelioma, perithelioma, cylindroma psammoma, cholesteatoma.

II. Hylic, or " Pulp " Tumours.

1. Of Epiblastic Origin.

(*a*) Typical : True neuroma, glioma.

(*b*) Atypical : Gliosarcoma.

2. Of Hypoblastic Origin.

Chordoma.

3. Of Mesenchymal Origin.

A. Mesenchymal Hylomas.

(*a*) Typical : Fibroma, lipoma, chondroma, osteoma, myxoma, leiomyoma, angeioma, myeloma.

(*b*) Atypical : Sarcoma with its various subdivisions—Fibrosarcoma, chondrosarcoma, lymphosarcoma, angeiosarcoma, etc.; of origin still debated, melanosarcoma.

B. Mesothelial Hylomas.

Rhabdomyoma.

It will be seen that only the autochthonous blastomas are considered in this table ; the teratomata and the heterochthonous blastomas receive separate treatment.

The classification is somewhat unwieldy, and suffers also from the disadvantage that it entails the introduction of a fresh nomenclature in a subject already overburdened in this respect. Nevertheless it is, in many ways, superior to all other systems.

It is complete in so far as it accommodates almost every type of tumour, and it avoids the difficulties arising from an imperfect understanding of histological details which are inherent in all morphological classifications.

It is of course a classification largely based on theories, and may, in the future, require modification in some respects. It agrees, however, with the known facts, and, above all, it helps us to appreciate and compare the relationships of the various blastomas from a biological as well as a morphological standpoint.

One of the most successful features of the scheme is the recognition of the great subclass of Transitional Lepidomata.

Certain tumours of this class, especially the endotheliomata and hypernephromata, show a bewildering variation in their histology, at one time being distinctly carcinomatous in structure, at another approaching the sarcomatous type. There has been infinite speculation as to their nature, but Adami's conception offers a reasonable explanation of the pleomorphism so characteristic of them. When growing slowly these tumours may behave as adenomata or carcinomata, but when growing rapidly they tend to lose their lepidic character—in obedience to the law that the properties which have been last acquired are the first to be lost—and assume the structure of the older hylic tissues.

Although this system is more scientific and suggestive than any other with which we are acquainted, yet, as Adami acknowledges, it is scarcely suitable for everyday use. From the clinical standpoint we have achieved a great deal if we can distinguish between the innocency and malignancy of any particular blastoma; this, together with the name of the tumour, or possibly a compound name indicating its structure, will fulfil all ordinary requirements.

In the description of the types of tumours which follows, the older nomenclature will be adhered to, and although all the more important varieties will be treated of, they will be grouped as convenience suggests, and in some cases their consideration will be deferred until we come to deal with the organs in which they usually occur.

For purposes of description we may divide tumours into the following groups :

The Innocent Connective Tissue Tumours.

Fibroma.	Chordoma.	Lymphoma.
Lipoma.	Osteoma.	Myoma.
Myxoma.	Odontoma.	Neuroma.
Chondroma.	Myeloma.	Glioma.

The Sarcomata, or Malignant Connective Tissue Tumours.
The Innocent Epithelial Tumours, Papilloma and Adenoma.
The Carcinomata, or Malignant Epithelial Tumours.
The Endotheliomata.
The Hypernephromata.
The Melanomata.
The Teratomata.

THE INNOCENT CONNECTIVE TISSUE TUMOURS

FIBROMA

A Fibroma is a tumour derived from fibrous connective tissue, and is therefore of very wide distribution. Almost every part of the body may be the seat of fibrous growths, but the majority of these tumours are found in connection with the skin and subcutaneous tissues, nerves, the sheaths of muscles and tendons, and in loose, submucous connective tissue. Though they are less common in other situations they are not infrequently encountered in solid organs such as the uterus, ovary, kidney, and breast.

The fibromata are innocent tumours, growing slowly and expansively ; they are sometimes multiple. In solid organs they compress the surrounding tissues, forming capsules from which they can be shelled out ; but when growing in the wall of a hollow viscus they have a tendency to project into the cavity as pedunculated polypi. This is particularly the case with the subcutaneous fibromata and with those of the uterus and the alimentary canal. As a rule, these tumours are covered by a layer of tissue derived from the organ in which they grow, but as the result of ulceration this investment may be absent, in which case the superficial layers of the polyp present a well-marked inflammatory reaction.

Macroscopically, fibromata form rounded, lobulated tumours varying considerably in consistency ; some are extremely dense and firm, while others are softer and more yielding. On section

the harder forms are extremely tough, and the cut surface has a white, glistening, whorled appearance often likened to "watered silk." The soft fibroma cuts much more easily, and the section is looser and more homogeneous; it is often moist and œdematous, and may show jelly-like areas of myxomatous change.

According to their consistence, then, two types of fibroma may be distinguished: (*a*) hard fibroma, and (*b*) soft fibroma, but intermediate forms are extremely common, and the same tumour, even, may vary in consistence in different parts. At its best the distinction is somewhat artificial, and the soft variety often owes its peculiar character to degenerative changes rather than to true differences in structure.

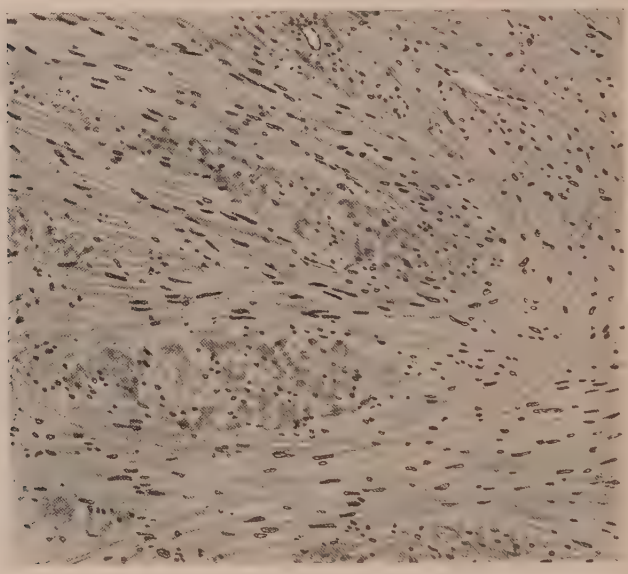

FIG. 14.—Fibroma of the breast. The tumour is composed of interlacing bundles of fibrous tissue, some of which are cut transversely.
Obj. 8 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

Microscopically (Figs. 14 and 15), fibromata consist of fibroblasts and bundles of formed fibrous tissue, and occasionally contain a few elastic fibres. There is a delicate stroma of connective tissue separating the lobules of the growth, and in it run the nutrient vessels. These are usually badly formed, and may consist of little more than a tube of endothelium surrounded by a dense connective tissue coat.

In the hard fibroma there is an abundance of formed fibrous tissue arranged in interlacing bundles, or as a dense felt-work, and the cells are compressed and comparatively few in number. The soft fibroma contains less formed fibrous tissue and is more cellular. Its tissue spaces are wider, and there is often an excess of œdema fluid. Rarely, multinucleated fibroblasts or giant cells may be met with in the soft tumours, but, when present, these generally indicate that the growth is more of the nature of a fibrosarcoma than an innocent fibroma.

Fig. 15.—Fibroma of the ovary.
Obj. 8 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

Fibrous tissue enters into the composition of many compound tumours forming, among others, fibro-adenomata, fibrolipomata, and fibromyomata. But apart from these true mixed blastomas, other tissues are met with in fibromata as the result of degenerative changes. Thus the hard fibromata are liable to undergo hyaline and calcareous degeneration, while the soft variety may show a tendency to myxomatous and, more rarely, fatty degeneration.

Closely allied to the fibromata, though differing from them in important particulars, are certain conditions of fibromatosis or fibrous tissue overgrowth. In some organs—the kidney, the prostate gland, and the breast—we may encounter localised areas

of fibrous tissue growth forming tumour-like nodules, which, however, are not encapsuled, but gradually fade off into the surrounding tissue. They are frequently multiple, are of slow growth, and often contain glandular elements which have become incorporated in the mass in the course of its growth. Rarely, a sarcomatous change may become apparent in one or more of these nodules, though this is always a late phenomenon.

Similar blastomatoid growths are met with in connection with other tissues of the body, and only by a careful examination is it possible to distinguish them from true blastomas.

In the conditions known as ***cheloid*** and ***molluscum fibrosum*** we have instances of this process as it affects fibrous tissue, which are of sufficient importance to merit a more detailed consideration.

Cheloid is the name given to an excessive production of cutaneous fibrous tissue, usually in association with some form of irritation, or at the site of injuries or operation wounds. Firm plaques or ridges are formed, having smooth, shining surfaces and sharp margins from which pointed processes extend into the neighbouring skin. As time goes on the tumours become harder and only increase in size very slowly if at all. There is a striking congenital predisposition to the condition, and in susceptible individuals the slightest injury may be followed by the formation of dense, often lobulated, fibrous tumours extending for some distance beyond the position of the original trauma. The nature of the irritant or injury, however, appears to be of some importance in determining the occurrence of cheloid, and Unna quotes a remarkable case where it followed tattooing with red dye, though not with blue.

Not only is there a personal predisposition to cheloid, but the racial incidence is also marked, and there is said to be a peculiar liability to it among negroes.

Although it has been claimed that the process may, in some cases, occur spontaneously, yet the amount of injury necessary to initiate it has been proved to be so slight that every instance must, in all probability, be regarded as reactive in nature.

After removal the tumours recur since the process is repeated in the operation scar.

Microscopically, a cheloid consists of dense bundles of collagen, often hyaline in appearance, between which lie a few compressed fibroblasts. In the early stages the tumour may be

more cellular, and there is usually a certain amount of cellular reaction around the cutaneous blood vessels adjacent to the periphery of the growth. Extension apparently takes place around the blood vessels of the deeper layers of the skin, and the process seems to be of the nature of a perivascular fibrosis affecting only these vessels. There is never any true encapsulation.

In ***molluscum fibrosum*** (v. Recklinghausen's disease) the blastomatoid process affects the fibrous tissue sheaths of the cutaneous nerves, resulting in the formation of subcutaneous nodules which show extraordinary variations in size and number in individual cases. The disease may be limited to one nerve and its branches, or it may be much wider in its distribution, so that the body becomes covered with hundreds of tumours varying in size from a pin's head to masses two or three inches in diameter. In the early stages the skin is freely movable over the nodules, but later it is fixed and smooth, and as growth proceeds the tumours become pedunculated from stretching of the surrounding cutis. While the nerve sheath as a whole is involved, it is in the endoneurium—the fibrous tissue surrounding the finer nerve filaments—that the chief change is seen. The epineurium is slightly thickened, as is also the perineurium, but the hyperplasia of the endoneurium is extreme, and results in wide separation of the nerve filaments, so that, although nerve fibres may be demonstrated entering or leaving the tumour, sections through the central portions commonly show only a moderately dense fibrous tissue, and the histology resembles closely that of a true fibroma.

Although in the majority of cases the neurofibromatosis is cutaneous in distribution, the deeper nerves are not entirely immune, but may present numerous, often massive, tumours along their course. Just as in the cutaneous nodules the fibrosis gradually extends to the skin, so, in the case of these deeper tumours, surrounding structures become invaded.

A similar change, though diffuse instead of localised, may occur in the nerves in certain parts of the body, giving rise to the condition known as ***plexiform neuroma***. This is usually seen in the nerves of the head and neck, but those of the limbs and trunk may be the ones to be affected, and even, in rare instances, the nerves of the sympathetic system. The nerves become extremely thickened, tortuous and elongated, and form visible tumours which, on palpation, give the impression of a collection of somewhat soft, nodular, anastomosing cords.

LIPOMA

Lipomata are slowly growing innocent tumours composed of adipose tissue. They have been described as occurring in many situations, but are most frequently met with in subcutaneous tissue, especially of the back and shoulders, in relation to serous and synovial membranes, and in muscles. More rarely, they may grow in the submucous coats of the alimentary canal and the larynx, in the periosteum of long bones, in solid organs such as the liver and the uterus, and in the meninges of the brain and spinal cord.

While the vast majority of these tumours arise from pre-existing fat cells, this is not invariably so, and they are occasionally found in parts which normally are entirely devoid of fat. In these cases we must suppose their origin to be from fat cells which have " wandered " in the course of the development of the body, " rests," in fact ; or, with greater probability, ascribe them to a process of metaplasia occurring in fibromata.

Lipomata vary very greatly in size, some being many pounds in weight. They are usually single, and, although simple spheroidal forms do occur, the majority present a marked lobulation. They are of a somewhat paler colour than the surrounding fat, and are always sharply encapsuled, being covered with a delicate coat of fibrous tissue from which rather coarser septa pass inwards between the lobules.

Microscopically, a lipoma is composed of fat cells of the adult type, though slightly larger than the cells of ordinary adipose tissue. Groups of cells are separated by delicate strands of connective tissue, and the tumour is nourished by well-formed blood vessels surrounded by a fairly abundant fibrous tissue sheath (Fig. 16).

Occasionally the cells of a tumour approximate more closely to the fœtal type of fat cell, and contain several small globules of fat scattered through the cytoplasm, instead of a single large one occupying the whole of the cell. It is in the more rapidly growing lipomata that this condition is seen.

Although lipomata are typically innocent tumours, they may assume malignant characters, when the fat cells are replaced by areas of rapidly growing sarcomatous tissue.

Fat enters into the composition of a variety of mixed tumours, giving rise to fibrolipomata (Fig. 17), myxolipomata, and angeiolipomata, and it is a common constituent of teratomata.

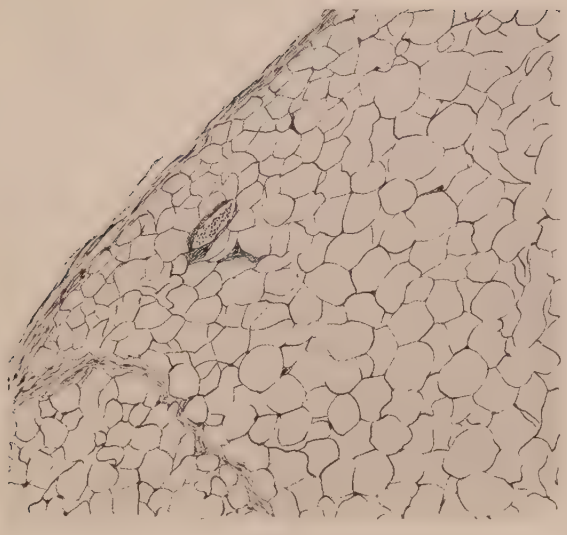

FIG. 16.—Lipoma of the breast.
Obj. 16 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

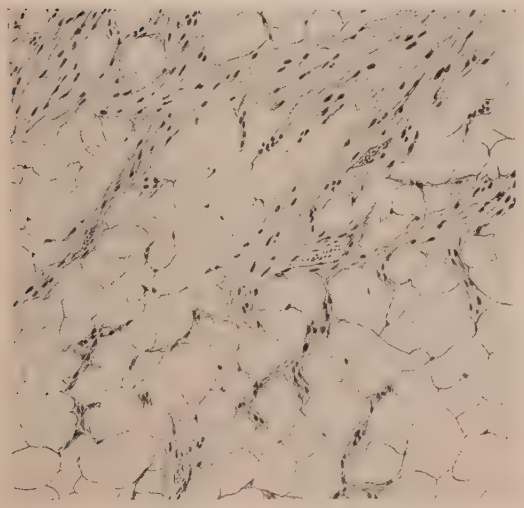

FIG. 17.—Fibrolipoma of the intestine.
Obj. 16 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

Apart from these mixed or compound neoplasms, the composition of lipomata is subject to alterations as the result of degenerative changes. The deposition of calcium salts may give rise to a dense, hard tumour, or softening may ensue from a diffuse mucoid degeneration of the cells. Occasionally, liquefaction may take place with the production of cysts filled with oily fluid.

As in the case of fibrous tissue, a localised blastomatoid overgrowth of fatty tissue, quite distinct from the subcutaneous and abdominal deposits of the obese, is not at all uncommon. It is particularly well seen in the " diffuse lipoma " of the neck and in the massive " perirenal lipoma."

MYXOMA

Myxomata are tumours composed of embryonic connective tissue similar to that present in the umbilical cord. They are among the rarest of all neoplasms, and while it is, perhaps, unjustifiable to deny their existence entirely as is sometimes done, it must be acknowledged that almost all the so-called myxomata are, in reality, instances of extreme mucoid degeneration in other forms of connective tissue growths. Fibromata, Lipomata, and Chondromata are all particularly liable to mucoid degeneration, and myxomatous tissue enters largely into the composition of many of the mixed tumours of the parotid gland and the kidney. Recognised authorities, however, have described pure myxomata as occurring in several situations, more especially in subcutaneous and subserous tissue, in muscle, in bones, and in the endocardium.

Such growths form rounded, lobulated, elastic tumours, which, on section, exude a glairy, mucinous fluid. They grow slowly and are encapsuled.

Microscopically (Fig. 18), they consist of connective tissue cells which are widely separated from one another and possess long branching processes. By the interlacing of these processes a delicate meshwork is formed, the spaces of which are filled with mucin. The blood vessels are usually capacious, and are surrounded by a varying amount of fibrous tissue. Frequently the vascular sheath is infiltrated with a considerable number of leucocytes, a condition which makes one rather sceptical of the true neoplastic nature of the growth. This histology may be

closely simulated by œdema occurring in a fibroma, or even in a mass of chronic inflammatory tissue, and failure to recognise this has led to a considerable degree of confusion, notably with respect to the " mucous polypi " of the nasal mucous membrane. These are in reality œdematous polyps, usually of inflammatory origin, and have nothing to do with true myxomata. A more complete histological examination will always make the diagnosis clear, for frozen sections of a myxoma become granular after

Fig. 18.—Myxoma of the jaw.
Obj. 8 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

treatment with acetic acid from precipitation of the mucin, and, in paraffin sections, mucin gives characteristic reactions with differential stains such as muci-carmine and thionin.

It sometimes happens that myxomata lose their innocent characters and assume malignant properties, growing with much increased rapidity and infiltrating surrounding tissues. These changes are reflected in the microscopic structure; the cells lose their branching processes and become essentially sarcomatous in type, while the mucin is absent or materially reduced in amount.

Bearing in mind the rarity of simple myxomata, and the fact that mucoid degeneration is a common phenomenon in sarcomata, it is difficult to be sure in these cases that the tumours

were not, from the first, sarcomata presenting advanced degeneration. But after the most rigid examination there remain a few instances where the malignant transformation of a myxoma seems the more reasonable explanation to adopt.

CHONDROMA

Chondromata are innocent tumours composed of hyaline- or fibro-cartilage. They are definitely encapsuled and of slow growth, and if of any size, are distinctly lobulated. On section they are of a bluish-grey colour and are semi-translucent. They are avascular and receive their nourishment from the blood vessels of the capsule. The central areas of large lobules may exhibit fatty or myxomatous degeneration, and in the variety known as the ossifying enchondroma there is a tendency to calcareous infiltration or even true bone formation.

Microscopically, the cartilaginous structure of the tumour is well maintained, though the cells may vary considerably in size and number, being small and numerous at the periphery where growth takes place, and larger and scantier in the deeper parts.

Tumours composed, wholly or in part, of cartilage are fairly common and may be roughly divided into three classes : (*a*) those growing in relation to bones, especially in the pelvis, the long bones, and the bones of the fingers ; (*b*) in situations where cartilage is normally present, such as the larynx ; (*c*) in organs where cartilage is absent, chiefly the ovaries and testicles and the salivary glands. In only a small proportion of these tumours, however, can we say with certainty that we are dealing with true chondromata. In the first place, we have to distinguish between true blastomas and cartilaginous hyperplasias, for blastomatoid growths occur in cartilage as in other tissues, and many of these tumours are examples of simple hyperplasias. In other cases, especially the cartilaginous tumours of the testicle or ovary, we are in reality dealing with mixed growths, or teratomas. In certain examples the cartilaginous element may dominate the picture, but a careful search will almost always reveal the presence of other varieties of tissues as constituent parts of the growth.

The majority of chondromata grow in connection with the epiphyseal junctions of the long bones. They are commonest

in childhood or adolescence, and often show a predisposition to occur in several members of the same family. It seems highly probable that many chondromata arise in islands of cartilage which have been separated from the epiphysis during the development of the bone ; and this supposition is borne out by the fact that a history of rickets or previous injury to the part is obtainable in a fairly high proportion of cases. Developmental errors are likewise held accountable for the growth of chondromata in situations where cartilage is normally wanting ; in the rare chondromata of the breast, for example, a " rest " from the developing body wall is postulated. Other explanations are, however, equally probable. In many cases, as we have seen, the tumours are really teratomata ; in others, it seems impossible to exclude a process of metaplasia occurring in the connective tissue of the organ.

Apart from malignant teratomas and chondrosarcomata, cases have been recorded in which chondromata, though apparently entirely innocent in their histological structure, have given rise to metastases, an accepted sign of malignancy. Now, there is no reason why a graft from an innocent tumour should not take root in a distant part of the host, for homologous transplantation of even normal tissues may be successfully achieved in a fair proportion of attempts. It is the spontaneous separation of grafts and their transference to other situations which is so suggestive of malignancy, and is so difficult to understand in the case of an innocent tumour. By virtue of their dense, elastic consistency, chondromata are not unlikely to ulcerate into veins, and when this happens the dissemination by the blood stream of minute fragments of the growth, or the actively proliferating cells of the perichondrium, is quite within the bounds of possibility. But it is probable that in most of the instances of the dissemination of a chondroma the tumours were not simple blastomas, but teratomas. The classical example of such a tumour is the malignant chondroma of the testicle, described by Paget, in a patient who afterwards died with secondary deposits in the lung. A further examination by Kanthack and Pigg demonstrated the presence of carcinomatous elements in the tumour, and these authors believed it to be a carcinoma with cartilaginous metaplasia of the stroma. Finally, Nicholson proved it to be a teratoma by discovering in it derivatives of all three primary germinal layers. With this example before us

we should, I think, regard with some suspicion the formation of metastases by a simple chondroma.

CHORDOMA

Chordomata are extremely rare tumours originating in the remains of the notochordal tissue, and are usually situated at the base of the skull, in the neighbourhood of the spheno-occipital synchondrosis, or in the sacro-coccygeal region.

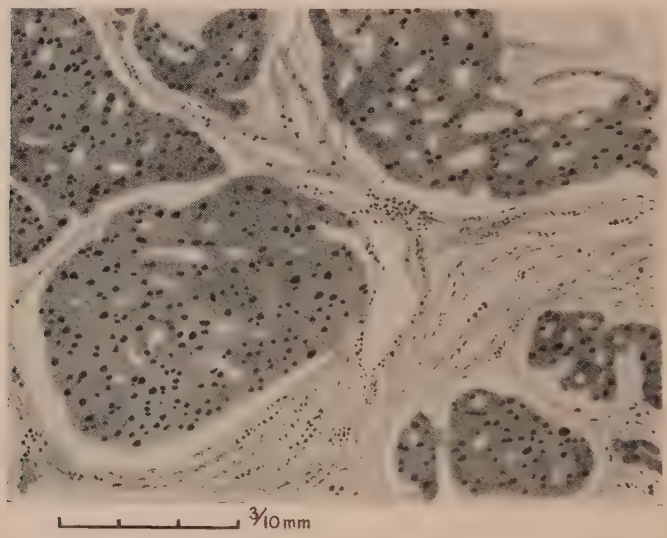

Fig. 19.—Section of a sacro-coccygeal chordoma, showing the alveolar structure of the tumour and the tendency to mucoid degeneration.

The majority of them appear to be malignant rather than innocent, but they grow slowly and rarely disseminate, though the cranial tumours, from their position, are always serious.

Histologically, they show some resemblance to chondromata, but are rather more cellular. They are alveolar in structure and show a tendency to undergo early mucoid degeneration.[1]

OSTEOMA

Pathological growth of bone is a common enough phenomenon both in connection with bony tissues and also in the soft parts,

[1] See Stewart, *Journal of Path. and Bact.* 1922, xxv. 1. p. 40.

but we are very far from a complete understanding of its nature. The technical difficulties associated with the histological examination of calcareous tissues are considerable, and possibly have been partly responsible for this state of affairs ; for we are content to employ such terms as " ossification," " exostosis," " calcareous degeneration," and the like, without troubling to attain to an accurate knowledge of the processes which have been at work.

We may assert with some confidence, however, that only a very few osseous growths are blastomas ; the majority are inflammatory in origin, or examples of calcareous infiltration, simple hyperplasias, or some similar change. Thus, the overgrowth of callus round an ununited fracture and the osteophytes of chronic osteomyelitis and rheumatoid arthritis are instances of bony growths which are certainly not blastomas. Similarly, in certain conditions of the soft parts of which the gradual replacement of muscle by bone in myositis ossificans and the ossification of the adductor muscles of the thigh in " riders' bone " are familiar examples, we are concerned with a process of metaplasia. Again, the infiltration of chronic inflammatory foci with calcium salts may simulate bone formation very closely, and may even suggest a new growth.

It is a fairly easy matter to distinguish between such conditions as these and true osteomas, but it must be remembered that the majority of bone tumours are very much more anomalous, and may be extremely difficult to interpret.

Osteomata are innocent tumours composed of bone and possessing all the histological features of that tissue : a calcareous matrix, typical cells with processes, and Haversian canals. Two varieties are recognised : the cancellous osteoma, and the compact or ivory osteoma. They grow slowly and expansively and compress the surrounding tissues, so that even when growing in bone their margins are always sharply defined.

Osteomata are almost entirely limited to the skeletal system ; only very rarely do they appear in the soft parts. They may arise in the interior of long bones and project into the medullary cavity, when they are known as ***enostoses***, or, and this is more common, they may grow as ***exostoses*** from the outer surface of the bone, and are often distinctly pedunculated. Occasionally osteomas are found among the muscles adjacent to a bone, from which, however, they are quite distinct. These ***parosteal exostoses*** are supposed to originate in groups of

periosteal osteogenetic cells which, by some means or other, have become detached from their normal situation.

Exostoses of long bones are composed of cancellous bone and often contain cartilage, indeed many of them appear to be ossifying enchondromata. They are frequently multiple, and numerous instances have been placed on record in which heredity was undoubtedly a strong factor in their etiology.

In the skull, exostoses are usually of the compact variety and are flat and sessile. An interesting form is the compact osteoma of the antrum of Highmore and the smaller sinuses. Although these tumours are very often inflammatory in origin, some of them are undoubted blastomas, growing progressively and causing destruction of the walls of the cavity.

A varying amount of bone may be found in slowly growing fibromata, but otherwise it is rare in innocent blastomas. It is, however, a fairly common constituent of teratomas, and frequently occurs in periosteal sarcomata.

ODONTOMA

Blastomas arising from the teeth are rare, though blastomatoid conditions of the dental sac and its contents as well as the neighbouring bone are not uncommon. What are apparently real blastomas are sometimes met with, and may be derived from the cement or the dentine. Fibromata may also arise in connection with the dental sac.

Odontomas are slowly growing tumours, though in time they may come to weigh several ounces.

An interesting form, the so-called epithelial odontome, is an epithelial tumour derived from the anlage of the enamel, and will be described subsequently.

MYELOID SARCOMA : MYELOMA

Tumours arising from bone but not composed of osteogenetic tissue, form an important group, but their pathology is still more or less obscure, and their nomenclature confused. Two types are recognised : (1) myeloid sarcoma, derived from the bone reticulum, and (2) myeloma, derived from the marrow.

Myeloid Sarcomata are never found apart from the skeleton. They are commoner in the lower limb than elsewhere, being

especially liable to attack the upper end of the tibia and the lower end of the femur. In the upper limb, the upper end of the humerus and the lower end of the radius appear to be the favourite sites. Besides the bones of the extremities, myelomata

FIG. 20.—Myeloma of the lower end of the femur. The tumour is almost entirely hæmorrhagic, there being only a thin shell of solid growth at one periphery.

may be found in the sternal end of the clavicle and the upper and lower jaws. They are extremely rare in other situations.

Except for the myeloid epulis which grows from the periosteum, myeloid sarcomata take origin in the interior of bones. As they grow, the bone becomes expanded and absorbed, and a rounded

tumour develops in the neighbourhood of the joint. The tumours do not infiltrate, but, nevertheless, the bone is gradually absorbed, and may give way under slight pressure, with the production of the important clinical sign of " egg-shell crackling." Occasionally the bone may be entirely deficient over certain areas, and,

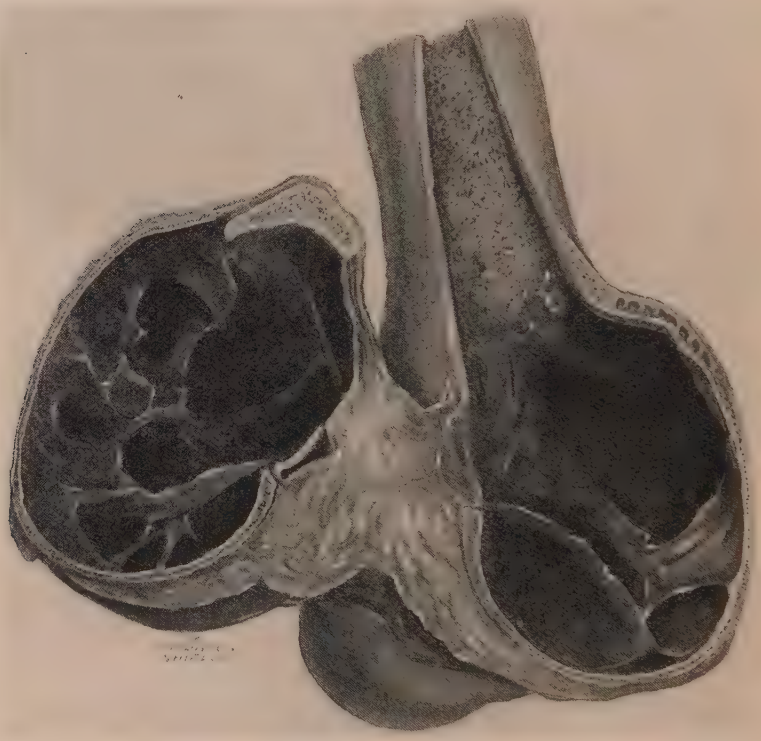

Fig. 21.—Cystic myeloma of the lower end of the femur.

since the tumours are highly vascular, pulsation may be perceptible at these points.

On section, myeloid sarcomata present a characteristic appearance. They are usually very hæmorrhagic and of a dark reddish colour (Fig. 20). As the result of old hæmorrhages and other secondary changes the colour may vary in different parts, and for the same reason there is often extensive cyst formation (Fig. 21). Spicules of bone may be scattered through the tumour, and at the margin there is sometimes a zone of firm white growth.

The *microscopic* structure of the myeloid sarcoma is distinctive and very curious when the innocent nature of the growth is taken into consideration. It consists of a basis of oval, indifferent cells of a decidedly sarcomatous appearance, and the giant cells which form the typical feature of the tumour. These are very numerous and variable in size ; scattered somewhat irregularly throughout them are fairly large, oval nuclei which may, as shown in the drawing (Fig. 22), be present in large numbers.

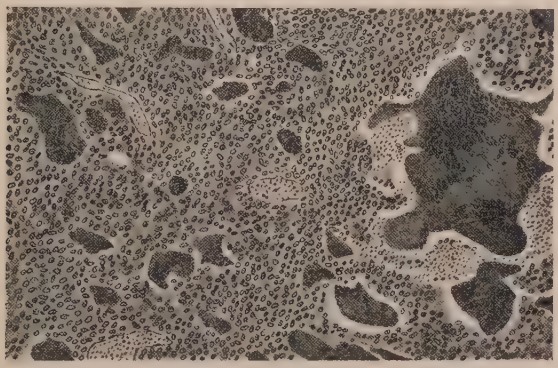

Fig. 22.—Section of a myeloma of the femur, showing a vascular sarcomatous-looking matrix and many multinucleated giant cells.
Obj. 8 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

S. C. Dyke has described the occurrence in a myeloid sarcoma of the head of the tibia of groups of " foam " or xanthoma cells containing anisotropic fat. The tumours are excessively vascular, being traversed by numerous delicate vessels, and they are consequently peculiarly liable to hæmorrhages.

During recent years a good deal of attention has been devoted to the pathology of these tumours. Whereas formerly they were universally regarded as malignant and treated by amputation, it is now generally held that they are relatively benign and may safely be dealt with by thorough curettage or local excision. Indeed, so far has the pendulum swung that there is a considerable body of opinion which regards them as manifestations of chronic hæmorrhagic or fibro-cystic osteomyelitis and not as true neoplasms. Stewart [1] holds that myeloid sarcoma is a true fibroblastic neoplasm arising in the fibrous reticulum of bone, and looks upon the typical giant cells as neoplastic osteoclasts. Dawson and Struthers [2] support this view.

[1] *Lancet*, 1922, ii. p. 1106. [2] *Edinburgh Med. Journal*, Oct. 1923.

If it is granted that we are dealing with a true neoplasm, it must be acknowledged that it is a very badly named one. On the assumption that the characteristic giant cells were abnormal megakaryocytes it was taught that the tumours originated in the marrow. This is certainly not so ; they are not myelomata in any sense of the term, but are fibroblastic growths derived from the specialised bone reticulum from which the normal osteoclast is formed. Similarly, they do not behave at all like true sarcomata. They undoubtedly have some local malignancy, but they seldom if ever disseminate. I have only met with one possible example of dissemination in which a small nodule having the typical histology of the myeloid sarcoma was found in the lung of a patient whose leg had been amputated above the knee joint some years before, but unfortunately no information was forthcoming as to the reason for the amputation. Inasmuch as true giant-celled sarcomata occur in the same situation as the myeloid sarcoma, the differential diagnosis between the two is of great importance. In the true sarcoma the giant cells vary greatly in size and in the number and size of their nuclei. They may contain abnormal mitotic figures, and transition forms can be traced between them and the smaller cells of the tumour which themselves are often in process of division. In the myeloid sarcoma, the giant cells are of the osteoclast type with regular nuclei ; and neither they nor the smaller cells exhibit signs of unusual activity.

Myeloma.—Blastomatoid growths of the bone marrow are of very great interest and complexity. We know nothing of their etiology and comparatively little of their pathology, but they are of importance as forming a link between certain ill-defined malignant tumours and the primary blood diseases. On the one hand we have diseases such as splenomedullary leukæmia and lymphatic leukæmia, in which the overgrowth of the bone marrow is thrown into shade by the constitutional symptoms and the change in the circulating blood : on the other are the conditions known as myelomatosis and chloroma, in which the blood changes are anomalous and irregular, and the formation of tumour-like nodes in connection with the bones is the chief feature in the case. From these processes to the round-celled and lymphosarcoma seems but a step, and we are confronted with a conglomeration of conditions on which it is impossible to dogmatise.

In ***Myelomatosis*** or ***Multiple Myelomata*** grey or reddish tumours occur in different parts of the skeleton but principally in the red marrow of the ribs, vertebrae or cranium. Several distinct tumours may develop simultaneously, or a solitary growth may be followed after a fairly short interval of time by others in different parts of the skeleton. The tumours give rise to absorption of bone, with the result that curvatures of the vertebral column and spontaneous fractures of the ribs may

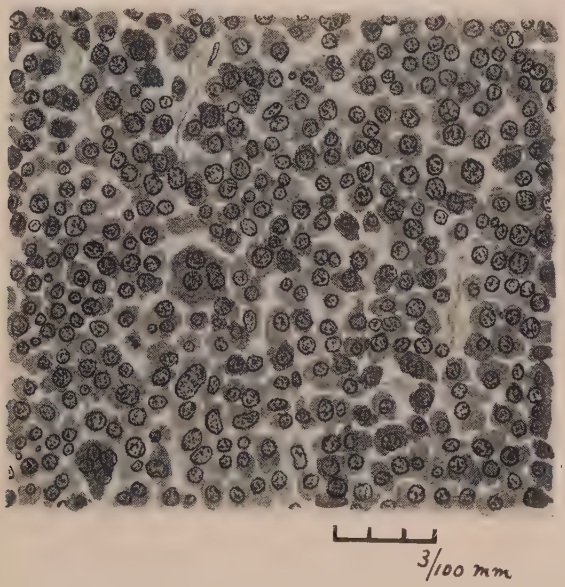

Fig. 23.—Section of a myeloma of the radius.

occur. With regard to the histology of the growth there is some difference of opinion. Some observers recognise the constituent cells as being myeloblasts, while others believe them to be plasma cells; probably more than one type of myeloma can occur. All, however, are agreed that the osteoclast type of giant cell, characteristic of the myeloid sarcoma, is not present. There is very little stroma, simply a delicate meshwork of fibrous tissue in which the cells are loosely packed (Fig. 23). The blood picture varies in different cases, but is usually that of a profound secondary anæmia.

The association of many of these tumours with an albumose

in the urine (Bence-Jones proteinuria) is well recognised, but another phenomenon is less generally known. This is the occurrence in some cases of myelomatosis of a strongly positive Wassermann reaction. I have twice been consulted in cases of undoubted myelomatosis in which syphilis was suspected because of the positive serum test. In neither case was there any history of syphilis, and at the autopsy of one of them no trace of this disease could be discovered. In one of the cases the sigma reaction was equally strongly positive.

Chloroma generally occurs in young people, and is characterised by the appearance of periosteal tumours in the skull, vertebræ, ribs, and sternum. When examined in the fresh state these tumours present a greenish colour which rapidly fades on exposure to the air. This colour may not appear in every one of the tumours, but is essentially the typical feature of the condition.

The tumours are in the nature of infiltrations of the periosteum by fairly large rounded cells of the lymphoid type, lying in a delicate connective tissue reticulum.

The blood picture is usually that of an acute leukæmia, but it is not constant either in the number or type of the circulating leucocytes.

LYMPHOMA

Lymphoid tissue is distributed very widely throughout the body, and readily undergoes hyperplasia in response to irritation and infection. Not only does the increase in size affect the established lymphatic glands, but fresh nodes, often of a highly atypical structure, make their appearance. Under these circumstances, it is easy to understand that the diagnosis of a lymphoma, *i.e.* a blastoma composed of lymphoid tissue, is a matter of some difficulty. Nevertheless a very few examples of this form of innocent neoplasm have been recorded.

Of much greater interest are the blastomatoid conditions of lymphadenoid tissue, and here we meet with much the same difficulties as confronted us in connection with the growths of the bone marrow. In the lymphadenoid enlargements associated with tuberculosis and Hodgkin's disease we are on sure ground, for the histological changes are well recognised; but in the more obscure conditions in which there is a local or generalised lymphoid hyperplasia with no distinctive microscopical features,

we are completely baffled. And in some of the blood diseases, notably lymphatic leukæmia, the tissue changes may so closely suggest a neoplastic process as to give rise to the utmost confusion.

It is obvious, then, that the subject is one of very great complexity, and, in the present state of our knowledge, to dwell on it would serve no useful purpose: all that is necessary is to indicate the questions that have to be answered in the future.

MYOMA

New growths of muscle are divided into two classes according to their origin from smooth or striated muscle: they are named respectively, Leiomyomata, and Rhabdomyomata.

Leiomyomata, in their incidence, rank high among the innocent blastomas, though their distribution is somewhat restricted. They may grow in any of the situations where smooth muscle is found, for example, the skin, the wall of the alimentary canal, and the bladder; and they are quite common, though always of a minute size, beneath the capsule of the kidney. Except in rare instances, these tumours are small and of little practical importance. They grow slowly, are frequently multiple, and are invariably encapsuled. They seldom give rise to any symptoms, though in the alimentary canal, where they tend to become polypoid, they may exercise some mechanical interference with function.

But in one organ, the Uterus, leiomyomata assume such notable proportions as to bring them into a class by themselves. The uterine "fibroids" are among the commonest of all innocent blastomas, and the most dangerous. They form tough, hard, spherical masses of a whitish or pale pink colour, and are sharply encapsuled. They originate in the substance of the uterine wall, and may always retain a covering of the normal muscle; but very frequently, as growth proceeds, they come to project above the external or internal surfaces, and are often pedunculated. They are nearly always multiple, and may be very numerous, though the several tumours differ considerably in size. On section, their density becomes apparent, and the cut surface closely resembles that of a fibroma. The tumours themselves are not highly vascular, though there are, as a rule, many large vessels in their capsules.

Microscopically (Fig. 24), leiomyomata are composed of interlacing bundles of smooth muscle fibres associated with a varying amount of fibrous tissue between the bundles. The two tissues are easily distinguished by their staining reactions, the muscle taking a yellow colour with van Gieson's stain, and a much brighter pink with eosin than the fibrous tissue. The nuclei, too, are quite characteristic, those of the muscle being long with blunt ends, whereas the fibrous tissue nuclei are shorter and more sharply pointed. The vessels of the growth are well

Fig. 24.—Section of a fibromyoma of the retro-peritoneal tissue. The tumour is composed of bundles of smooth muscle fibres (1), mingled with fibrous tissue in which lie the blood vessels (2).
Obj. 16 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

formed, and run in the fibrous tissue. In some tumours the fibrous tissue simply provides a scanty framework for the muscle fibres; but in others, especially the uterine myomata, it forms a considerable proportion of the whole tumour mass, and apparently grows equally with the muscular elements, so that the name "fibro-myoma" is fully justified. Speaking generally, it may be stated that the larger the tumour is the more fibrous tissue it will contain.

Degenerative changes are not infrequent in myomata, and in the case of the important uterine fibroid they have been studied in some detail.

One of the commonest changes is an excessive proliferation of the fibrous tissue elements, leading to an increase in density and firmness of the tumour, and though this is scarcely a retrogressive change the process is usually known as "fibroid degeneration." The fibrous tissue is also affected in hyaline degeneration. Here the muscle fibres are untouched, but the fibrous tissue loses its structure and becomes converted into a homogeneous mass of hyaline material. Myxomatous degeneration is fairly common, and here again the fibrous tissue is the one to be involved. This form of degeneration may be so extensive as to result in the production of large cysts filled with mucinous fluid. Calcareous degeneration may be primary in a slowly growing tumour, or it may follow on a localised anæmic necrosis. It may be central or peripheral in its distribution. Necrobiosis, or red degeneration, appears to be due to the thrombosis of the capsular vessels, and is often associated with pregnancy. When it occurs the tumours become softer, and on section are of a deep red colour. Septic infection with sloughing and necrosis may occur in the submucous variety of uterine myomata. Finally, it must be noted that simple atrophy of uterine myomata may take place after the menopause.

Leiomyomata are typically innocent tumours, and some authorities go so far as to assert that under no circumstances can they undergo a malignant change. This view, however, seems to be untenable. Fibroids of the uterus do undoubtedly become sarcomatous; the point at issue is whether the change takes place in the muscular or the fibrous elements. It is not easy to furnish absolute evidence in either direction, but there is no reason why the muscle fibres should not give rise to sarcomas, and often the histological appearances strongly suggest that they do. And I have seen one case of myosarcoma of the intestine in which it was almost certain that the malignant process started in a simple myomatous polyp.

Smooth muscle fibres rarely occur in mixed tumours, with the exception of the teratomata of the ovary and the testicle, where they are quite common.

Blastomatoid growths of smooth muscle are not of very great importance. Shattock has drawn attention to an overgrowth of the muscle fibres of the walls of arteries and veins in a fibroma, apparently blastomatoid in nature; and I have had the opportunity of examining a subcutaneous tumour of the

leg in which a similar process had given rise to a considerable mass.

In the familiar senile hypertrophy of the prostate, again, there is usually a notable hyperplasia of the muscular elements of the gland.

A very interesting tumour, the "adenomyoma" of the uterus, has many of the characters of a myomatosis. Adenomyomata are diffuse growths of smooth muscle, usually situated in the posterior uterine wall. They are peculiar in that they contain, imbedded among the muscle bundles, regular gland

Fig. 25.—Section of an adenomyoma of the uterus. The tumour is composed of interlacing bundles of smooth muscle fibres (1), among which lie gland tubules embedded in a cellular stroma (2).

Obj. 16 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

tubules surrounded by cellular connective tissue, and exactly resembling those of the uterine mucous membrane (Fig. 25). Sometimes these tumours are extra-uterine, being situated on the posterior vaginal wall, or the wall of the pelvic colon or rectum. The pathology of the condition is unknown. Some observers believe that the epithelial tubes are direct down-growths from the uterine glands, which excite the proliferation of the muscle fibres. Others hold with von Recklinghausen that both epithelial and muscular elements are derived from the remains of the wolffian duct. Probably the former is the more likely explanation in the case of the intra-uterine growths, for the glands of the normal uterus may extend very deeply among the muscle

bundles of the wall, and a direct continuity between the tubes of an adenomyoma and the glands of the mucous membrane has been demonstrated in several cases. It is more difficult to account for the origin of the vaginal and intestinal adenomyomata, though it has been claimed that they are also derived from similar outgrowths of the uterine glands.

Rhabdomyoma.—Innocent tumours entirely composed of striated muscle are extremely rare, but they have been recorded as occurring in the heart, in the skeletal muscles, in the uterus, the kidney, and the œsophagus.

It is doubtful whether mature striated muscle can ever give rise to tumours, and the generally accepted view is that rhabdomyomata always arise from fœtal rests.

The normal structure of striated muscle is never fully reproduced in such tumours, but the muscle cells are always irregular, both in size and shape, and frequently contain several nuclei. Further, cross striation is often absent altogether, or present only in parts of the fibre.

Striated muscle, sometimes quite well formed, is occasionally found in mixed tumours, especially in the renal sarcomata of infants ; and a few cases of true rhabdomyosarcoma have been described.

NEUROMA

The neoplasms of nerve tissue form a complicated group which is rendered still more difficult by reason of the various blastomatoid processes to which this tissue is liable. Much work, however, has been done on this subject in recent years, and it is possible to recognise some distinctive neoplasms without much difficulty. Although some of these tumours are definitely and, indeed, highly malignant, it will be convenient to discuss them all at this point.

Since the nerve cell is the essential constituent of the neurone, it follows that a neuroma must contain not only nerve fibres but also nerve cells ; otherwise it cannot be said to possess that independent existence which is the chief characteristic of blastomas. So, at the start, we may exclude those conditions of fibrosis which we have already treated of in the description of the fibromata, and also such processes of hyperplasia of nerve fibres as are met with in the " amputation neuroma," for these have no relation to true blastomas.

The primitive neuroectodermal cell from which the whole nervous system is derived, differentiates early into the neurocyte, from which the specific nerve tissue is developed, and the neuroglioeyte which produces the glial or supporting tissue. Certain of the neurocytes migrate ventrally to form the sympathetic chain and the paraganglia, penetrating into the cortex of the

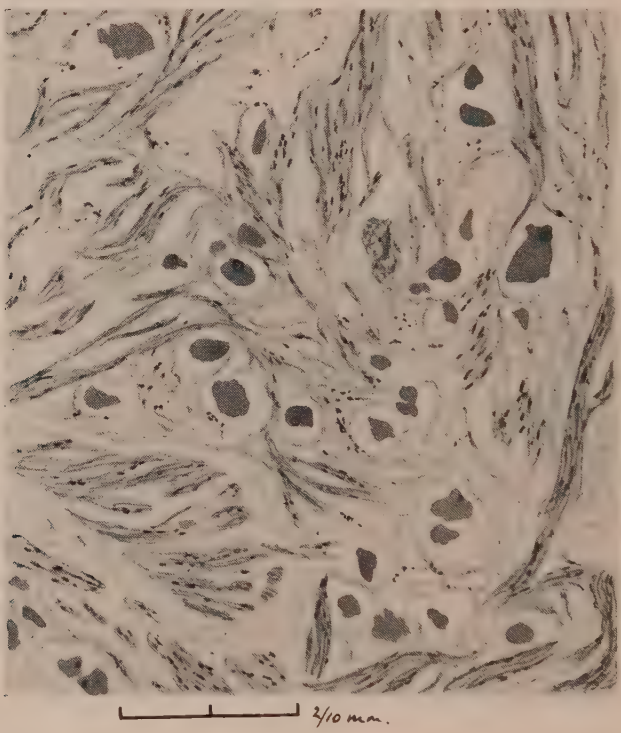

Fig. 26.—Ganglioneuroma of the suprarenal, showing nerve fibres and ganglion cells.

adrenal to form the medulla. Later, in the adrenal and the other paraganglia these neuroblasts differentiate into the ganglion cells and the chromaffine cells. Corresponding to these developmental stages, neurocytomata (one example), neuroblastomata, ganglioneuromata, gliomata, and paragangliomata or chromaffine tumours have been described. As might be expected, however, many of these tumours are not pure but contain elements representing nerve cells in different stages of development.

Ganglioneuromata are exceedingly rare tumours found in connection with the sympathetic ganglia of the thorax and the abdomen, the medulla of the suprarenal gland, and the skin; in the last situation they are believed to arise in the ganglia in the walls of the arteries. They occur in young subjects, and are, apparently, always congenital in origin. They may attain to a considerable size, but are usually innocent.

Microscopically (Fig. 26), they contain ganglion cells in large numbers together with nerve fibres which are often well formed and may even be medullated.

Neuroblastoma.—This tumour seems to be of wider distribution than the ganglioneuroma. It occurs in the central

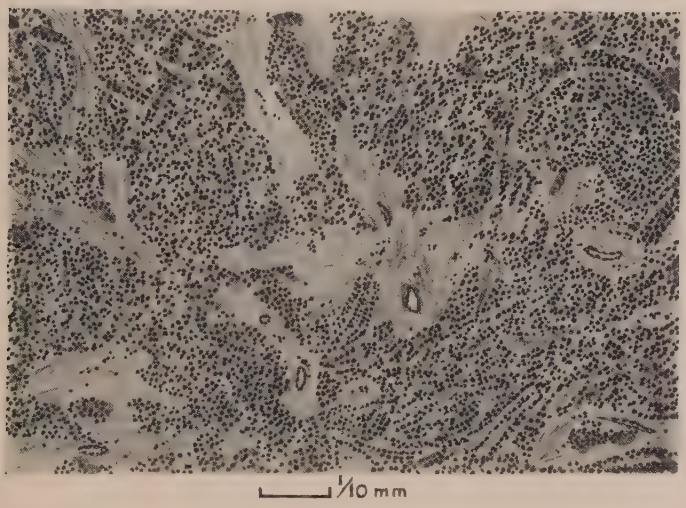

Fig. 27.—Section of a neuroblastoma of the suprarenal showing the formation of fibrils.

nervous system and its outgrowths as well as the sympathetic system, but most often arises in the adrenal. It is a rare tumour, but is probably more common than is generally supposed.

It is, as its name implies, composed of cells which show a certain degree of differentiation in that their cytoplasm is prolonged at one point into a fibril, which recalls the axon of the adult nerve cell. As a rule, these tumours are malignant and give rise to metastases. Their cellularity and their power to

form fibrils alter with the rate of growth, and in rapidly growing examples it may be impossible to demonstrate conclusively their nature. In the more typical forms the fibrils are either arranged in bundles or else as small, spherical, felted masses surrounded by a ring of cells, to which the term "rosette" is applied (Figs. 27, 28). In similar tumours of the retina the cells of the "rosette" are often grouped round a lumen rather than a

Fig. 28.—Neuroblastoma of the retina showing the typical rosettes (1).

felted mass of fibrils. As this structure suggests the ependyma such tumours have been called gliomata or gliosarcomata, but this seems an unnecessary distinction.

Paraglioma.—This tumour occurs chiefly in the adrenal and the carotid body (Fig. 159). It is usually innocent and is composed of chromaffine cells in various stages of differentiation. Occasionally nerve elements are also present.

As is only to be expected in so highly differentiated a tissue, nerve elements, recognisable as such, are not found in the

commoner mixed tumours. They occur, however, with some frequency in the teratomata (Fig. 29).

FIG. 29.—A teratoma of the ovary showing a mass of glial tissue (1) containing a central canal lined by columnar epithelium, and groups of ganglion cells with nerve fibres. It suggests the attempt to form a spinal cord with ganglia.

GLIOMA

The neuroglia, or supporting tissue of the central nervous system, is developed from the epiblast; but, as Adami points out, it has assumed the characters of "pulp" tissue, and tumours derived from it may be considered as being in the connective tissue group. Nevertheless, the cells of a glioma may be of a distinctly epithelial type, rendering a diagnosis a matter of much difficulty.

Gliomata are found only in the central nervous system and its outgrowths, and the great majority occur in the brain.

As a rule, they form somewhat soft tumours, though, as in the case of the fibrous tissue growths, hard and soft varieties are recognised. They may grow to a considerable size, and their margins are usually indistinct. In colour they vary from a yellowish-white to a greyish-pink. They are very subject to degenerative changes as the result of alterations in their vascular

supply, so that areas of softening, with subsequent cystic degeneration, and hæmorrhages, are common.

Microscopically (Fig. 30), gliomata consist of glial cells and fibrils. The cells are usually small, rounded, or oval, and have a single deeply staining nucleus. The fibrils are extremely delicate and easily break down, so that the matrix of the tumour rarely presents a distinctly fibrillar appearance, but is commonly homogeneous or granular. In the fresh state the fibres react specifically to certain staining methods, but this power rapidly

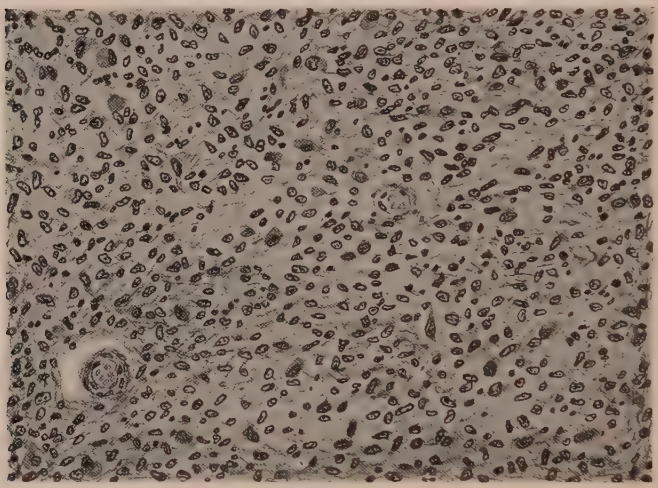

Fig. 30.—Section of a glioma of the cerebrum. The tumour is highly cellular, the cells varying in size and shape; the groundwork is composed of interlacing neuroglia fibrils.

Obj. 8 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

becomes lost; and since the tumours are usually met with in the post-mortem room, it is rarely possible to obtain good microscopical preparations. It has long been a debated point as to whether the fibrils retain a direct continuity with the cell, or whether they become separated and merely lie in apposition to it; probably the former view is correct.

The cells of a glioma do not always conform to the normal type, but sometimes resemble epithelial much more than glial cells. They may be isolated, when they bear a striking resemblance to ganglion cells, or they may be arranged in solid alveoli. Sometimes they occur as linings to cystic spaces, so

much suggesting the cells of the ependyma that the name "ependymoma" is given to tumours having this histology.

Gliomata are innocent tumours, though, from their position, they frequently prove fatal. Occasionally they undergo a malignant change, growing rapidly as highly cellular tumours with little attempt at the formation of fibrils. Since the nature of a glioma can only be proved incontrovertibly by the demonstration of glial fibres, it follows that in many tumours the diagnosis must remain doubtful. This is especially so in gliomata occurring outside the central nervous system. Thus, innocent gliomata may grow in connection with the retina or the medulla of the suprarenal gland: more commonly, such growths are malignant, and give rise to metastases. These tumours used to be, and by many people still are, called gliosarcomata; other authorities regard them as being neuroblastomata.

An interesting feature in connection with gliomata is the fact that a history of injury is obtainable in a number of cases. It is true that a single trauma may initiate the malignant process; but, on the other hand, it is quite possible that many so-called gliomata are, in reality, blastomatoid conditions. From analogy with other tissues, there is no reason why the glia should be immune to progressive hyperplasias, indeed, such a gliomatosis is well recognised in the "Hypertrophy of the Pons" of children; and it is quite possible that our conception of what constitutes a glioma may be considerably modified in the future.

THE SARCOMATA

The sarcomata are malignant tumours derived from the connective tissues. They form a large and important class, and, on the whole, present problems of greater complexity to the histologist than do any of the other types of neoplasms.

They are essentially cytomata or cell tumours, and their elements never, except in the most rudimentary manner, combine so as to form distinct tissues. This is one of their most striking differences from the innocent connective tissue tumours, for these, as we have seen, are histiomata, and reproduce, although atypically, the structure of the tissues from which they arise. There are, no doubt, malignant representatives of each of the connective tissue histiomata, but their cells are so embryonic or vegetative

in character that it is, often enough, impossible to determine their derivation.

Apart from the embryonic nature of their cells, sarcomata possess in a high degree all the properties we have come to associate with malignancy : thus, they grow with great rapidity, infiltrate surrounding tissues, and give rise to widespread metastases.

In characteristic examples of either class, then, we should have no difficulty in distinguishing between innocent and malignant connective tissue tumours. But it must not be forgotten that our classifications are, after all, purely arbitrary ; there is always a zone where one order fades into the next. So it is with the sarcomata. Tumours of a comparatively slow growth and a certain degree of differentiation possess, to some extent, the characters of both innocent and malignant blastomas, and it may not be possible to decide in which class to place them.

A further and more troublesome difficulty in the diagnosis of sarcomata is found in the likeness these tumours bear to processes of inflammation and repair. In both conditions the histological appearances may be similar, *e.g.* an embryonic type of cell, immature blood vessels, and an ill-defined margin of growth. In inflammatory conditions, of course, the type of cell is not, as a rule, uniform ; but yet the resemblance between granulation tissue and a round-celled sarcoma is notorious, and I have knowledge of a case in which a gummatous tongue was amputated under the impression, from an imperfect microscopic examination, that it was malignant.

An anomalous connective tissue reaction may also be seen occasionally in connection with carcinomatous growths. I have encountered very striking examples of a highly malignant-looking proliferation of the stroma in epithelial growths of the breast, the gall-bladder, and the epiglottis, in which I have been entirely at a loss to define the nature of the process.

It will be seen, therefore, that the study of sarcomata demands a considerable histological experience, and, even then, the diagnosis of individual cases may be purely a matter of opinion. Each observer has his own standards of what constitutes a sarcoma, and it seems quite probable that we must be prepared for a considerable readjustment of our ideas in the future, with the elimination of not a few of the conditions which we are now content to place in this group.

Nevertheless, in typical examples the histological features are sufficiently characteristic. The tumours are composed of actively growing undifferentiated cells, which are not closely applied to one another, but are surrounded by an intercellular matrix. In some tumours this matrix is more obvious and complete than in others, but in every case it can be demonstrated by appropriate methods of fixation and staining. At the same time, there is only a moderate amount of stroma, and the tumours are highly cellular. Occasionally, in the alveolar sarcomata, the stroma is more abundant, and broad bands of it may enclose solid masses of the tumour cells, so that the structure may bear some resemblance to that of a carcinoma. This formation, however, is rare, and the cells are usually scattered thickly and diffusely through the growth. It is to this absence of stroma that the peculiarly homogeneous naked-eye appearance so typical of the sarcomata is due, for there is no scaffolding to break the continuity of the tumour cells.

The nuclei of sarcoma cells show changes reflecting the vital activity of the tumours. Mitoses, both typical and atypical, are numerous, while direct divisions and multiplication of the nuclei in single cells are not uncommon. Nuclear degenerations may be met with, but not so frequently as in the epithelial tumours, for it is more usual for the whole cell to die if the nutrition becomes imperfect.

The blood vessels of a sarcoma are ill-formed and consist of little more than a tube of endothelium. At the best they are invested by but a meagre sheath of connective tissue, and as a rule they course through the tumour in close contact with the cells which, in some cases even, themselves seem to line the vascular spaces. This delicacy of the blood vessels is responsible for the hæmorrhage which so frequently takes place into the substance of the growth.

The growth of sarcomata is peripheral and infiltrative, the tumour cells extending irregularly along fascial planes and lymphatic spaces. Metastatic deposits occur both by the blood stream and the lymphatics. From the intimate relation of the tumour cells to the vascular spaces, it is easy to understand the extension of the growth to the venous system : in most cases the spread is by embolism, but direct permeation of the larger veins is not unknown. Similarly, lymphatic spread takes place by permeation and embolism, and although this form of

dissemination is obscured by the more obvious vascular one, invasion of lymphatic glands takes place quite often in these tumours.

As a natural consequence of the rapidity of their growth, and the extreme delicacy of their vessels, we usually find degenerative changes in sarcomata of any magnitude. Rupture of a vessel with extravasation of blood into the substance of the tumour is a very common happening, so much so that the probability of any excessively hæmorrhagic tumour being a sarcoma is generally recognised. As the result of this hæmorrhage, or possibly from thrombosis of some of the larger veins, considerable areas of the tumours may undergo quiet necrosis. A similar necrosis may follow in those tumours in which growth is so vigorous that the formation of new vessels fails to keep pace with it. A frequent change, though one often overlooked, is fatty degeneration. This is present in the majority of rapidly growing tumours, very many of the cells containing fat globules of varying sizes. Oedema and mucoid degeneration are common in fibrosarcomata, affecting chiefly the matrix; the tumours become soft and elastic, and large cysts filled with glairy fluid may be formed.

We have seen that it is not possible to adopt a purely histogenetic classification of sarcomata, however greatly this is to be desired, for as often as not it is impossible to determine from which variety of tissue the tumours are derived. In some cases, it is true, the tumour cells show a considerable degree of differentiation, so that we can readily recognise their nature; but in others, the more embryonic and undifferentiated forms, this is not so, and we are forced to fall back on a system based on the morphology of the cells. Thus, we are accustomed to recognise the following varieties: small and large ***round-celled sarcoma; oat-celled sarcoma;*** small and large ***spindle-celled sarcoma;*** and ***polymorphic*** and ***giant-celled sarcoma***. These forms are to be regarded as the most malignant representatives of the connective tissue tumours, for in them anaplasia reaches its height, and their energies are directed entirely towards growth.

With a lower degree of anaplasia and a more fully differentiated cell, it becomes possible to adopt the more satisfactory histogenetic grouping, since in these cases we are able to distinguish malignant neoplasms corresponding to the innocent ***fibroma, lipoma, myxoma, chondroma, osteoma, lymphoma, myoma,*** and ***glioma.***

These tumours occupy an intermediate position between the extremes of innocency and malignancy: it is often possible to trace in them the development of the anaplastic characters, and a more extensive study of them may be expected to add materially to our knowledge of the derivation of the more malignant types.

Small Round-Celled Sarcoma (Fig. 31).—This is the most primitive type of blastoma and also the most malignant. It is composed of small round cells, loosely applied to one another, and surrounded by the merest trace of a reticulated matrix. The

FIG. 31.—Small round-celled sarcoma infiltrating muscle. (1) Sarcoma cells; (2) muscle fibres.
Obj. 8 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

cells resemble very closely the lymphocytes of the blood, but are slightly larger. They have a relatively large, round, deeply staining nucleus, sometimes situated eccentrically, which is surrounded by a scanty layer of cytoplasm. The tumours are highly vascular, being supplied by numerous delicate capillaries around which the cells are prone to collect. They exhibit retrograde changes to a marked degree. Hæmorrhages are almost invariably present, while many of the cells can be demonstrated to contain fat globules. It is also quite common for large areas of necrosis to occur in which the cells lose their staining reactions, and only a suggestion of the structure of the tumour can be made out.

Dissemination by the blood stream is widespread and rapid, and generalisation of the growth occurs very early; for this reason the tumours are practically always fatal in a few weeks or months. Local infiltration along tissue spaces and fascial planes is also extremely vigorous, so that operative treatment is of little use.

It is commonly believed that the small round-celled sarcoma is derived from the fibrous connective tissue of the body, but

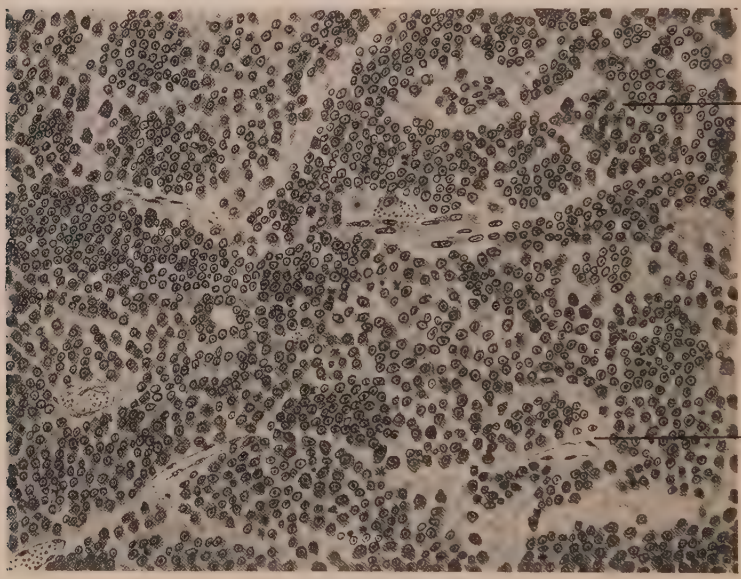

Fig. 32.—Large round-celled sarcoma of muscle. (1) Sarcoma cells, some in process of division; (2) delicate stroma containing thin-walled capillaries.
Obj. 8 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

it is not unlikely that it represents the embryonic stage of all the tissues. Certainly there is nothing in its distribution to indicate its origin, for it may occur in any situation, though it seems particularly prone to arise in the fascia of muscles.

Large Round-Celled Sarcoma (Fig. 32).—The large round-celled sarcoma is also of wide distribution, occurring in connection with muscle, skin, and many of the viscera. It is a highly malignant tumour, though it does not disseminate quite so rapidly or so widely as the small-celled form.

It differs from the small round-celled sarcoma in other

important features. Its cells are larger, and possess much more cytoplasm. They are not always entirely spherical, but may be almost polygonal in shape, and the nuclei are clearer and less dense. The matrix is still scanty, but shows a tendency to increase, and there is often a definite fibrous stroma which may be so marked as to result in the production of a distinctly alveolar structure.

In the viscera the large round-celled sarcoma occurs as a diffuse growth, but elsewhere, in as much as it has a certain degree of organisation of structure, it tends to form definite tumours of some size.

Degenerative changes are as common in this variety as in the small round-celled form, and are of a similar character. Dissemination takes place by means of the blood stream, and metastases are also usually present in the neighbouring lymph glands.

Oat-Celled Sarcoma.—This variety of sarcoma is somewhat rare. It is composed of short oval cells of a regular and distinctive form, aptly described by the name "oat-shaped," which lie in a scanty matrix and are nourished by delicate capillaries. We have not sufficient evidence to associate these tumours with any particular type of tissue, but they are usually found in fibrous tissue, the sheaths of muscles, and the periosteum, and they may arise from the connective tissue of any of the viscera.

They possess a high degree of malignancy, but are more amenable to treatment than are the round-celled sarcomas.

They may exhibit any of the degenerative changes which have been described.

Spindle-Celled Sarcoma (Fig. 33).—The majority of the more anaplastic sarcomata fall into this group, which, again, is subdivided according to the size of the constituent cells of the tumour. Such a subdivision, however, would appear to be of little practical value. It is purely arbitrary, for there is scarcely the same distinction between the small and large spindle-celled growths as there is in the case of the round-celled sarcomas, and it affords us little or no indication as to the biological properties of the tumours.

The spindle-celled sarcomata occur in almost every tissue and organ of the body. The small-celled group are generally believed to arise from the fibrous connective tissues, while the larger-

celled forms are more particularly associated with periosteum and smooth muscle.

The spindle-celled sarcomata are composed of fusiform cells, which vary a great deal both in length and breadth in different tumours ; each cell contains a single long, oval nucleus, centrally situated. An occasional multinucleated or giant cell may sometimes be encountered, but these are rather rare in the pure spindle-celled sarcoma.

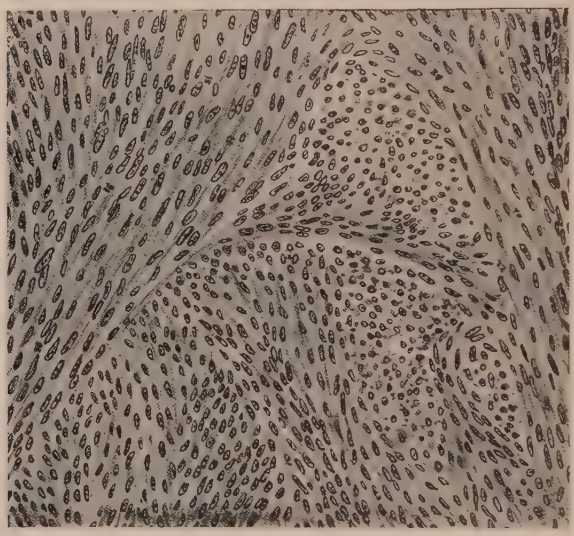

Fig. 33.—Section of a spindle-celled sarcoma of the forearm. Obj. 8 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

The cells are separated from one another by a fine homogeneous matrix, but are at the same time grouped together in bundles which lie in different planes, forming a close, interlacing feltwork. This structure becomes very evident in the microscopic section, for some of the fasciculi are cut transversely, others longitudinally, but it is too fine to be revealed to the naked eye. Not infrequently, fine strands of connective tissue may be scattered irregularly through the tumour, producing an imperfect, microscopic lobulation.

The tumours are nourished by numerous capillary vessels which lie in close contact with their cells ; so intimate is the relationship that the tumour cells seem sometimes to replace the vascular endothelium.

The spindle-celled sarcomata tend to form somewhat firm tumours, having a fairly sharply-defined margin, and often attaining a considerable size. Individual tumours vary in their rate of growth and in their power of forming metastases, but, as a rule, dissemination occurs later than in the types previously described. The common retrograde changes affect these tumours with some frequency, but while they are less liable to hæmorrhages than the round-celled forms, they very often exhibit advanced mucoid degeneration.

Polymorphic-Celled Sarcoma.—In its general characters this type of sarcoma does not differ greatly from the preceding group. Its cells, however, instead of being of a uniform type, exhibit an astounding variability in size and shape ; and large and small, rounded and polygonal, oval and fusiform cells may all be present in the same microscopic field. Giant cells containing several nuclei are also frequent constituents of these tumours, indeed they may be the dominating feature, and it is owing to the occurrence of such giant-celled sarcomata that the present confusion exists with respect to the myelomata of the bone marrow.

Polymorphic-celled sarcomata are commonly found growing from bones, but they may occur elsewhere, and I have met with particularly striking examples in the breast and the uterus.

Turning now from the pure sarcomata to the intermediate forms, we have to deal with a less malignant, more highly differentiated neoplasm, in which it is possible to distinguish the nature of the constituent cell. All grades of cell differentiation are met with until a point is reached where it becomes impossible to state definitely that the tumour is really a sarcoma, possessing malignant properties.

It will be readily understood that the histology of these tumours exhibits great differences as we pass from the malignant to the more innocent types, and that there is room for a considerable divergence of opinion in the interpretation of their microscopical characters. Only by long experience can standards, sufficiently just as to make an expression of opinion of value in difficult cases, be acquired.

Fibrosarcoma (Fig. 34).—The typical fibrosarcoma is a fairly firm tumour, having a comparatively slow but infiltrative growth. Only rarely, and then quite late, does it form metastases. It is more cellular than the innocent fibroma, and its

cells are larger, more irregular in shape, and sometimes multinucleated; nevertheless, they tend to produce fibroglia fibres, and there is always more matrix than in the pure sarcomata.

Its vessels are unformed and are often quite large, and the tumours may become soft and cystic from œdema and mucoid degeneration.

With increased malignancy the general histology approaches that of the spindle-celled sarcomata.

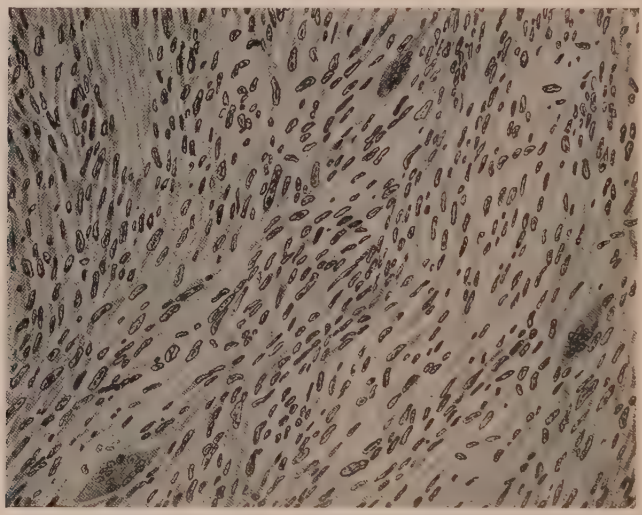

Fig. 34.—Section of a fibrosarcoma. The tumour is composed of large spindle cells, with occasional giant cells. There is much production of collagen. Obj. 8 mm. apochrum. Comp. oc. 6. Tube length, 160 mm.

So long as their malignant character is realised, it matters little whether we class the more anaplastic tumours among the pure sarcomata or the fibrosarcomata; but at the other end of the scale it becomes necessary, and increasingly difficult, to distinguish between simple fibromata, fibrosarcomata, and those conditions of fibromatosis to which attention has already been drawn.

Liposarcoma.—We have seen that all sarcomata are prone to undergo fatty degeneration, and we must distinguish such tumours from the true blastomas derived from adipose tissue. Liposarcomata do exist, though they are undoubtedly rare. They may arise directly from fat cells, or may result from malignant transformation of the cells of a simple lipoma.

They are composed of cells of an embryonic type containing numerous small fat globules in their cytoplasm: these globules become dissolved out in the preparation of ordinary paraffin sections, when the protoplasm has a vacuolated, "foamy" appearance.

In the more malignant liposarcomata the cells revert to the undifferentiated, sarcomatous type, and only in the older parts of the tumour is it possible to determine their true character.

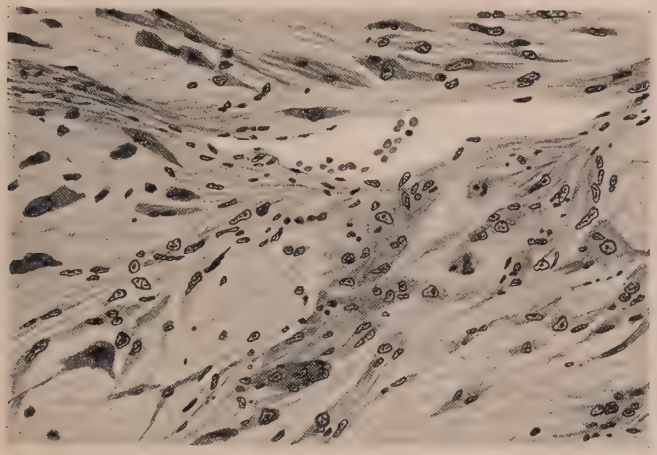

FIG. 35.—Section of a myxosarcoma of the thigh. The cells are irregular in size and shape, and there is much formation of mucin. A large thin-walled capiliary is situated in the upper part of the section.

Obj. 8 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

Myxosarcoma (Fig. 35).—In this class, again, we must distinguish between a retrograde process in a pure sarcoma and a true malignant blastoma of myxomatous tissue.

Mucoid degeneration is common in the spindle-celled and fibrosarcomata, and the more slowly growing tumours may present large cysts filled with glairy, mucoid fluid. The process seems to start in the intercellular matrix, which swells up and separates the tumour cells till eventually the structure becomes completely disorganised.

The great majority of the so-called myxosarcomata come into this category, but, very rarely, malignant tumours are encountered whose cells have the power of secreting mucus. These true myxosarcomata have a fairly high degree of malignancy, and form metastases with some readiness.

Chondrosarcoma (Fig. 36).—The chondrosarcoma is derived from cartilage, and its cells retain, more or less imperfectly, the power of reproducing the structure of the parent tissue. It occurs only in connection with bone or in those parts where cartilage is normally present; in other situations cartilage-forming tumours are to be regarded as being teratomata.

The chondrosarcomata usually form rather massive tumours, and in their naked-eye appearances closely resemble the innocent chondromata; they are, however, much more liable to retrogressive changes, especially mucoid degeneration.

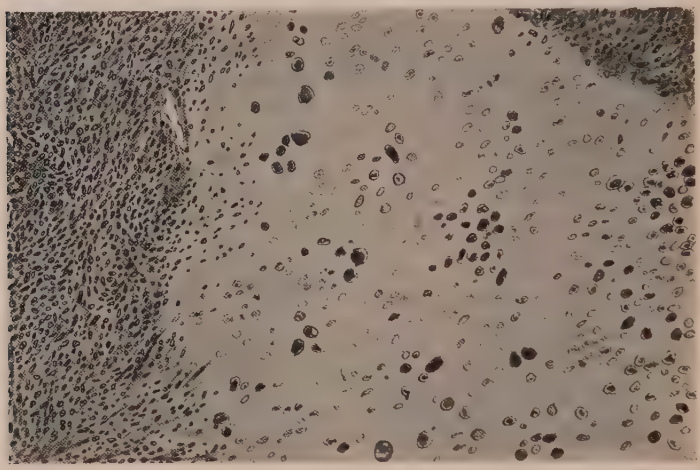

Fig. 36.—Section of a chondrosarcoma of the larynx showing atypical cartilage with sarcomatous tissue at the periphery.
Obj. 16 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

Microscopically, the structure varies with the degree of malignancy of the tumour. In the less active forms large lobules of unmistakable cartilage are produced, and the diagnosis can only be made by an examination of the growing margin. Here there is a zone of cellular, distinctly sarcomatous-looking tissue, showing, in the number of mitotic figures present, evidence of rapid growth. In the more malignant types the sarcomatous element predominates, and islands of imperfectly-formed cartilage occur only irregularly. Frequently, over considerable areas, there is no cartilage at all, only an excess of myxomatous matrix.

The chondrosarcomata do not grow with very great rapidity, and though they infiltrate and destroy the adjacent tissues, they do not usually disseminate at all widely.

Osteosarcoma (Fig. 37).—As its name implies, the osteosarcoma tends to produce true bone; and, as we should expect from a consideration of the other tissue-forming sarcomata, all grades may be met with between the innocent osteoma, composed entirely of bone, and the fibro- or spindle-celled sarcoma, devoid of any recognisable tissue.

FIG. 37.—Section of an osteosarcoma showing the formation of spicules of bone (1) among the sarcomatous tissue (2).
Obj. 8 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

Macroscopically, the presence of bone may be quite obvious, for it may form a great part of the tumour mass, but in other cases it may only be revealed by making thin sections through the whole substance of the growth. The presence of bony matter, however, does not prove the tumour to be an osteosarcoma, for it may be simply the result of calcareous degeneration in a slow-growing fibro- or chondro-sarcoma. Again, a periosteal sarcoma sometimes erodes the surface of a bone irregularly so that small spicules become separated and incorporated in the substance of the tumour, thus giving the impression of acutal bone formation.

On the other hand, a tumour may form osteoid tissue consisting of trabeculæ, almost typical in every respect except that there is no deposition of calcium salts in the matrix; these of course will not be apparent on naked-eye examination.

The *microscopical* features of an osteosarcoma are often most complex. The sarcomatous element is usually of the spindle-

celled type, but the cells may be shorter and stouter, oat-shaped or even polymorphic. In the neighbourhood of the bone trabeculæ the cells are arranged as, and behave like, osteoblasts. Quite commonly the osteosarcoma contains an appreciable admixture of cartilage, when the name osteochondrosarcoma is applied to the tumour.

The anaplastic types of this tumour grow rapidly and form metastases, but the bone-producing forms increase in size at only a moderate rate, and often remain entirely localised. The metastases may be pure sarcoma, or may themselves produce bone. The former is more usual, but I have notes of a case of an osteosarcoma of the humerus, an enormous tumour which ulcerated extensively, where at the autopsy the only secondary growths were two small nodules in the infraclavicular glands of the same side, and one other nodule in the opposite lung ; all of these consisted entirely of bone.

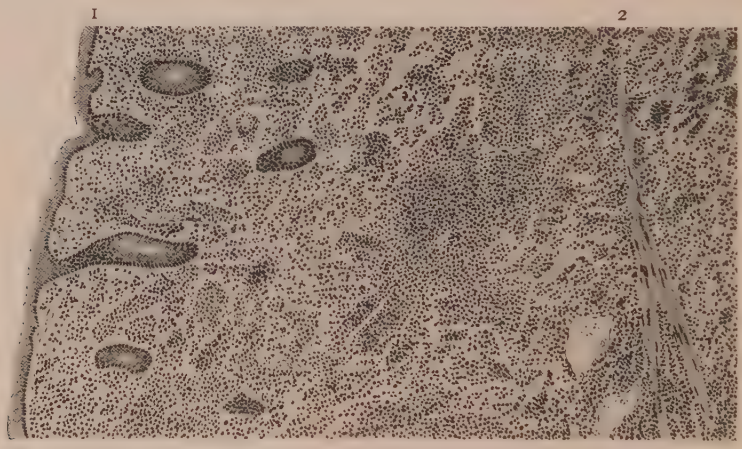

Fig. 38.—Lymphosarcoma of the intestine. The tumour is composed of small round cells lying in a delicate connective tissue reticulum. (1) Epithelium ; (2) muscularis mucosæ.

Obj. 16 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

Lymphosarcoma (Fig. 38).—The lymphosarcoma bears a certain likeness to the round-celled sarcoma, but both in its histological characters and its mode of growth it possesses sufficiently distinct features to bring it into a class by itself.

The tumours are derived from lymphoid tissue, and might be expected to have a wide distribution ; as a matter of fact, the majority of them occur in three situations, viz. the lymphoid

tissue of the alimentary canal, especially of the cæcum ; in the anterior mediastinum ; and in the tonsils and the cervical lymphatic glands.

Macroscopically they form large, firm tumours, with rounded, irregular surfaces ; on section they present a whitish homogeneous appearance, broken by areas of hæmorrhage and degeneration. The growth is infiltrative, and metastases readily form in the neighbouring lymphatic glands, though rarely in other situations unless by direct extension from the primary growth or the secondary deposits in the glands. This lymphadenoid dissemination is very characteristic of the lymphosarcoma.

Microscopically the tumours resemble lymphadenoid tissue, being composed of small round cells lying in a fine fibrous meshwork. The growths are well supplied with delicate capillary vessels, and the likeness to a round-celled sarcoma may be great. A careful examination, however, will reveal the presence of an abundant, though delicate, fibrillar intercellular substance, much more abundant than in the round-celled sarcoma, and will render the diagnosis clear.

Two important examples of lymphosarcoma require some further notice.

The intestinal lymphosarcoma sometimes grows to a considerable size, and, together with the adjacent glands, forms a large mass. The growth spreads underneath the mucous membrane and does not, except in advanced cases, cause any ulceration, but multiple nodules are frequently present in the wall of the gut. In the later stages the peritoneal coat becomes invaded, and extension takes place into the surrounding connective tissues ; but even then sufficiently wide removal offers a fair chance of success.

The mediastinal tumours are supposed to arise in the remains of the thymus gland, but, since they may occur in the posterior mediastinum, any lymphoid tissue must be regarded as a possible source of origin. The tumours often attain a great size, invading the lungs, and spreading to the abdominal lymph glands (Fig. 39). Both the intestinal and the mediastinal tumours conform to the usual histological type, but in the latter I have noticed a tendency on the part of the cells to assume a distinctly oval form.

In discussing the innocent lymphoma, attention was directed to the close association between lymphoid overgrowth and other

conditions, especially certain of the leukæmias. I have recently had an opportunity of making a post-mortem examination in a case which illustrated this point particularly well. During life

Fig. 39.—A mediastinal tumour from a child. The tumour has infiltrated the root of the neck and the mediastinal tissues, surrounded the costal cartilages (1) and invaded the parietal pericardium (2). There is extention to the glands of the posterior mediastinum (3).

the patient exhibited the blood picture and the general clinical features of a typical case of lymphatic leukæmia. At the autopsy there was found to be only moderate enlargement of the

lymph glands all over the body ; but there was a very massive tumour of the anterior mediastinum, which infiltrated the lung and the chest wall, and was proved by microscopical examination to be a lymphosarcoma.

Leiomyosarcoma (Fig. 40).—It is not often possible to be sure that a sarcoma is derived from smooth muscle, though it is quite likely that many spindle-celled sarcomata are muscular in origin. But occasionally one meets with a tumour which, though it shows no naked-eye peculiarities, can be diagnosed

Fig. 40.—Section of a leiomyosarcoma. The tumour is composed of bundles of smooth muscle fibres, supported by a fibrous tissue stroma.
Obj. 16 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

with certainty from its microscopical characters as a malignant growth of smooth muscle. Personally, I have only encountered them in the alimentary canal.

The distinguishing features of such tumours are the nuclei and the arrangement of the cells.

The nuclei may be numerous, but are often scanty as compared with the ordinary spindle-celled sarcoma ; they are longer than usual, and have blunt or rounded ends ; mitotic figures are often present.

The cells are arranged in bundles as in the spindle-celled sarcoma, but they do not interlace so closely, being separated by a distinct connective tissue stroma in which run the nutrient vessels. Often it is possible to make out a longitudinal striation in the cells, but this is not invariable.

The leiomyosarcomata are highly malignant tumours, forming metastases in lymph glands and in the viscera.

Rhabdomyosarcoma.—Pure malignant growths of striated muscle are rare, though they are occasionally found in the genito-urinary tract and elsewhere: teratomata containing striated muscle fibres are probably more common.

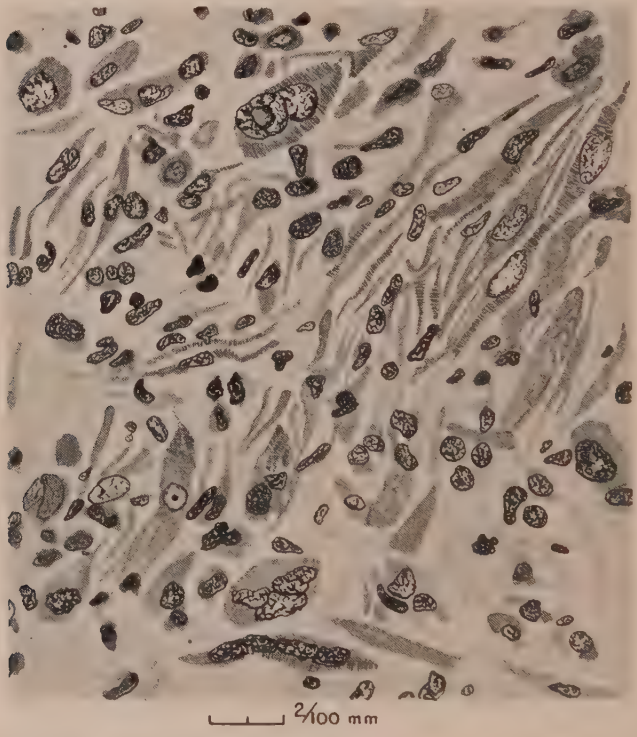

Fig. 41.—Section of a rhabdomyosarcoma showing the irregularity of the tumour cells with imperfect cross striation.

The histology of these tumours is very variable (Fig. 41). They are composed for the most part of large irregular cells, often possessing long, broad processes, and surrounded by a fairly abundant intercellular substance. Giant cells are not uncommon.

To establish the diagnosis it is necessary to demonstrate cross striation in the cytoplasm, and this may be extremely difficult to do. It may be present in the processes or in the body of the

cell, or it may be absent altogether. In my own collection I have sections of three or four tumours in which, though the general features strongly suggest a rhabdomyosarcoma, no striation can be made out.

Gliosarcoma.—Of the gliosarcomata little need be said. In characteristic examples the tumours are extremely cellular and contain few fibrils ; enough, however, to establish the diagnosis. In the more malignant forms it may be impossible to demonstrate any neuroglia fibrils at all, and one can only hazard a guess as to their nature from their situation and general appearance.

Certain tumours of the retina and the adrenal gland are particularly interesting. They grow rapidly and form widespread metastases, and, both to the naked eye and microscopically, are very like small round-celled sarcomata. But in fairly fresh preparations it is often possible to show that the cells possess long, thin processes ; also, they have a tendency to adopt a " rosette " arrangement. These tumours are usually regarded as being gliosarcomata, but, as has already been mentioned (p. 103), it is more probable that they are malignant growths of embryonic nerve cells, or neuroblastomata.

THE INNOCENT EPITHELIAL TUMOURS: PAPILLOMA AND ADENOMA

Before entering upon a description of the epithelial tumours, it is necessary clearly to understand the nature of the tissue with which we have to deal.

The epithelial cells form the lining membranes of the surfaces of the body, and certain solid glandular structures derived from them ; they therefore possess the features to which Adami has directed attention as being peculiar to all lepidic tissues. Whatever their arrangement may be, whether spread out as a covering to a surface, or collected together as a solid organ, epithelial cells are always in absolute contact with one another ; there is no intercellular substance such as we have seen is universally present in all hylic or connective tissues.

The collections of cells are supported by a scaffolding or stroma of connective tissue which renders it possible for any particular epithelium to assume its distinctive arrangement.

Not only does the connective tissue support the epithelium,

but it is of vital importance to its nutrition, for all the blood and lymphatic vessels are contained in the stroma, are, in fact, integral parts of it.

It is obvious, then, that epithelium cannot exist apart from connective tissue, and further, that the growth of the stroma must keep pace with that of the epithelium.

It is in view of this intimate relationship that benign neoplasms of epithelium have been described by some authors as ***fibro-epithelial*** tumours. Such a title, however, does not seem to have much real justification for its use, for it does not express the essential nature of the tumours, but rather creates confusion. After all, the proliferation of the epithelium is the thing that matters; the accompanying growth of fibrous tissue is purely subservient to it. It is not denied that combined epithelial and connective tissue tumours do occur, tumours in which both elements progress equally, but they are rare; a more careful examination almost always enables us to distinguish one or other element as the predominant partner.

The innocent epithelial tumours are histiomata; that is to say, they reproduce, although atypically, the structure of epithelial tissue. According to the mode of growth, therefore, two main types exist—the papilloma corresponding to the surface or covering cells, and the adenoma corresponding to those of the secretory or glandular organs.

In the papilloma the cells are situated externally, being arranged around an internal core of connective tissue; in the adenoma they form tubules or solid masses, which are embedded in, and surrounded by, the connective tissue stroma.

In the latter group it is not uncommon for the tubules to dilate into cysts of varying size, and for the lining epithelium to project into the cavity in a papillomatous manner, giving rise to a ***papillary cystadenoma.***

Although they exhibit differences in growth and behaviour depending upon their individual structure, papillomata and adenomata agree in their general properties, and these may be conveniently discussed now.

In the first place, these tumours are innocent: they progress slowly, and, though they may compress surrounding tissues, they never infiltrate; and they never form metastases.

The cells conform closely to the normal, and while their growth is often exuberant, it is never so uncontrolled as to make

it impossible for us to determine the nature of the tissue from which the tumour was derived.

In the amount of stroma and the character of the blood vessels there are, of course, variations in different tumours; but the vessels are usually well formed, and they are always separated from the tumour cells by a definite layer, however delicate, of connective tissue.

Degenerative changes are not particularly common in the epithelial histiomata, and such retrograde changes as do occur are often nothing more than a perversion of the normal physiological activity of the cells. Thus, in the squamous papilloma of the skin there may be an excessive production of keratin, the so-called "horny degeneration"; and extreme activity of the secretory cells of an adenoma may result in "mucoid" or "colloid" degeneration.

The surface of a papilloma is sometimes injured by pressure or friction, and ulceration may result from this mechanical irritation; from their situation these growths are also liable to inflammatory changes following infection with septic organisms. Hæmorrhage into the substance of the growth from the rupture of a vessel occasionally takes place in the large adenomata, but anything in the shape of massive necrosis is quite rare. Fatty degeneration of the cells may occur, and in the more slowly-growing tumours the stroma may show myxomatous or hyaline degeneration, and even calcareous infiltration.

The question as to whether benign epithelial tumours ever assume malignant characters has long been the subject of speculation and discussion, and even now complete unanimity has not been reached. Some authorities regard such a change as being not only possible but comparatively common; others hold that an adenoma always remains innocent. On theoretical grounds there seems no reason why the cells of an adenoma should not take on a malignant growth, in fact we should imagine them to be particularly liable to do so; and a similar process undoubtedly occurs in the connective tissue blastomas. Further, while fully recognising the difficulties attendant on the perception of the absolute beginnings of a malignant growth, one occasionally obtains histological preparations which seem to prove the matter beyond all possible doubt. Figs. 42 and 43 illustrate such a preparation. The tumour was a small adenoma of the thyroid and was clinically innocent. On examination the middle of the

tumour was found to be occupied by a solid whitish growth showing central necrosis. Histologically, the central growth has all the characters of a carcinoma, and there can be no doubt that it originated within the adenoma, and presumably from it. A similar association of a carcinoma with an innocent papilloma is illustrated in Figs. 135 and 136.

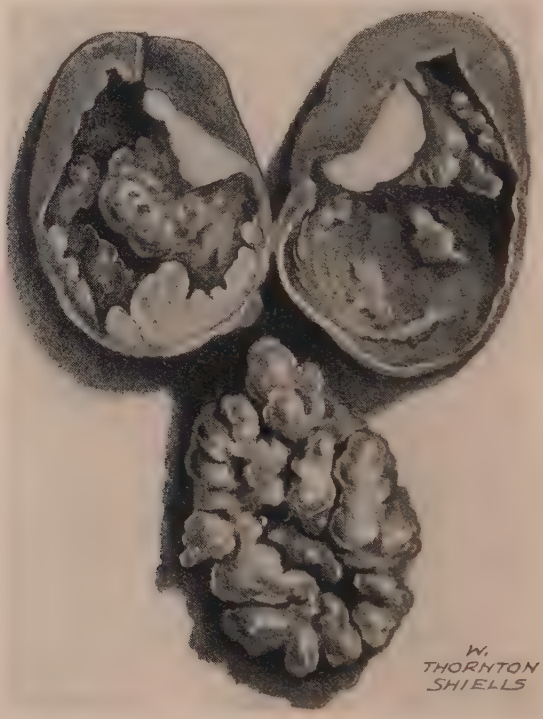

Fig. 42.—An adenoma of the thyroid showing malignant change. The centre of the adenoma is occupied by a homogeneous pale, friable growth, much of which broke away when the tumour was cut.

It is well to recognise, however, that innocent and malignant tumours may grow concurrently in the same organ, especially an organ such as the breast which is peculiarly liable to neoplastic processes of various kinds. Most pathological museums could supply specimens illustrating this phenomenon.

It is interesting to note that adenomata may be the seat of secondary malignant growths, either as the result of local infiltration, or from the progressive development of a malignant

embolism. Thus, I have observed metastases in a thyroid adenoma in cases of carcinoma of the tongue and the breast, where the malignant cells were undoubtedly transported by the blood stream.

In studying the benign epithelial blastomata we are again confronted with the difficulty to which reference was made in the description of the connective tissue tumours—that of distinguishing the true blastomas from the false. Simple hyperplasias, and reactive processes to bacterial and other irritants, may closely simulate true papillomata and adenomata; and though by recognising the exciting cause we can often be certain of the blastomatoid nature of a tumour, in the absence of any etiological factor it may be impossible to arrive at a definite conclusion one way or another.

Papilloma

Papillomata may be divided into three groups according to their origin, from (*a*) the skin, (*b*) the mucous surfaces, (*c*) the lining of cysts.

(*a*) The cutaneous papilloma or wart is a dense hard tumour, usually attached to

Fig. 43.—Section of the tumour illustrated in Fig. 42. The section includes the capsule of compressed thyroid tissue (1), the adenoma (2), and the central carcinoma (3). Note the compression and infiltration of the adenoma by the carcinoma. For the most part the carcinoma is undifferentiated, but at the periphery there are small acini or vesicles.

FIG. 44.—Simple papilloma of the skin. (1) Normal epithelium at the margin of the papilloma; (2) connective tissue papilla; (3) hyperplastic epithelium; (4) superficial keratinisation. Semi-diagrammatic. × circ. 16.

FIG. 45.—Horny papilloma of the skin. (1) Normal epithelium at the margin; (2) hyperplastic epithelium; (3) dense superficial layer of keratinised epithelium. Semi-diagrammatic. × circ. 16.

the skin by a broad base; its surface is finely fissured, but the individual processes are never very long or distinct (Fig. 44). Occasionally it may grow into a veritable horn from excessive keratinisation of the superficial cells (Fig. 45). The tumours are often multiple, and commonly show a moderate degree of pigmentation.

(*b*) The mucous or soft papilloma presents a distinctly villous appearance. It is composed of long delicate processes attached

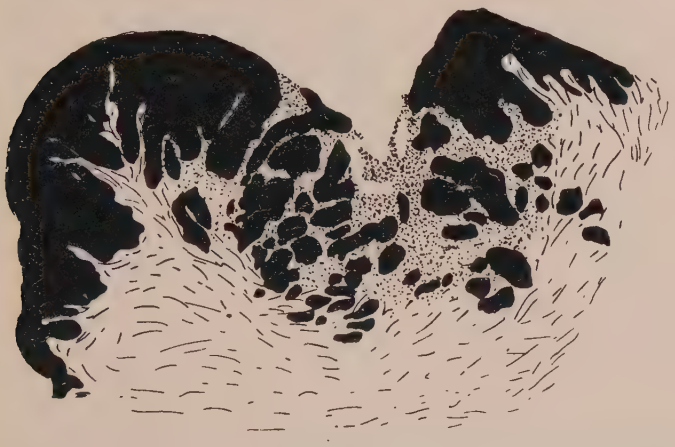

FIG. 46.—Malignant papilloma of the tongue. Compare with Figs. 44 and 45. The overgrowth of the superficial epithelium is not so marked, but columns of epithelial cells are passing downwards among the deeper tissues. Semi-diagrammatic. × circ. 16.

around a somewhat slender central stalk (Fig. 47). Such tumours are found mainly in the alimentary canal, especially the lower bowel, and in the urinary bladder, though they may, of course, occur in many other parts of the body. In the bladder they are extremely soft and bear quite a striking likeness to certain seaweeds; and they frequently involve large areas of the mucosa.

Another type of soft papilloma, characteristically seen in the intestine, consists of a solitary thick finger-like process, hundreds of which may be present in the condition known as colitis polyposa.

A soft papilloma, intermediate in structure between the above, forms the commonest tumour of the larynx, and may also occur on the tongue.

FIG. 47.—Section of a villous papilloma of the bladder. (1) Papilla cut longitudinally, showing connective tissue core with covering of stratified epithelium; (2) papilla cut transversely, showing central blood-vessel in connective tissue core.
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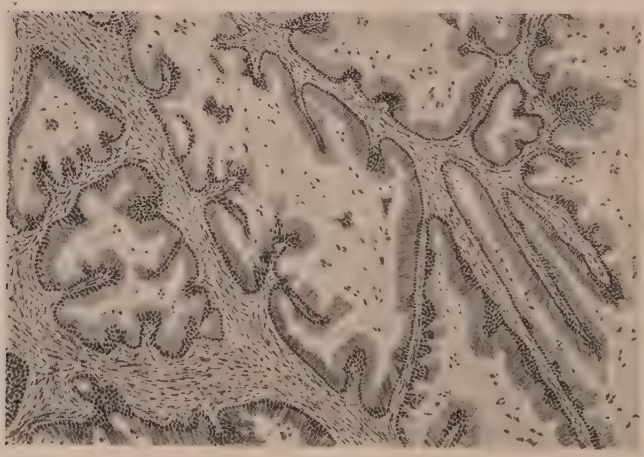

FIG. 48.—Papilliferous cystadenoma of the ovary. The tumour contains large cystic spaces, lined with columnar epithelium, and filled with mucoid fluid and cell debris. From the lining epithelium numerous papillomatous ingrowths project into the cavities of the cyst.
Obj. 16 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

(*c*) The intracystic papilloma (Figs. 48 and 49) may consist of a coarse branching growth, or it may more approach the villous type. It is seen to perfection in cystic ovarian tumours and in cysts of the breast.

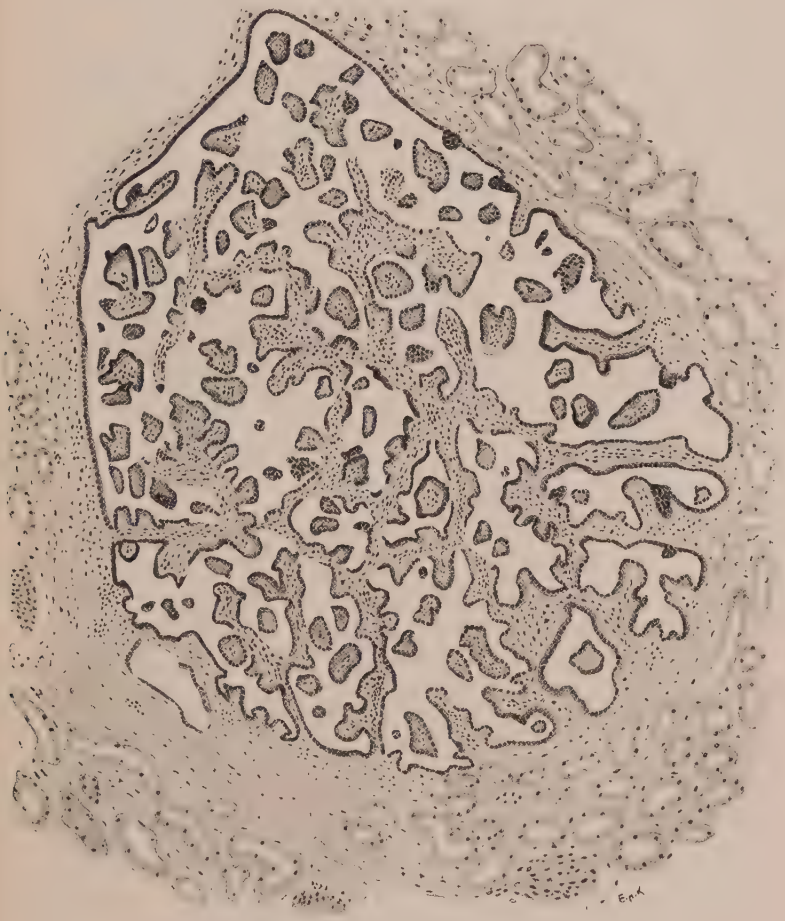

FIG. 49.—Papillary adenoma of the kidney.
Obj. 16 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

Microscopically the simple papilloma is composed of a layer of cells disposed around a core of vascularised connective tissue. At its inception the tumour consists simply of a budding or folding of the superficial epithelium, the two layers of ingrowing cells being separated merely by the basement membrane which

accompanies them. As growth proceeds, fibrous tissue and capillary blood vessels insinuate themselves between the layers of the basement membrane, and the structure becomes complete. Secondary outgrowths of the epithelium and stroma will give rise to the more complex compound papillomata. In the majority of cases the cells are several layers thick ; and though they are usually well formed and typical, this is not always so, and they may differ widely from their normal prototypes. In the intracystic papilloma there is often only one layer of cells.

The squamous papilloma shows a considerable variation in structure. It may conform to the typical arrangement, or it may largely consist of a simple heaping up of the epithelium with a very imperfect formation of stroma.

The rectal papillomata have usually a complex adenomatous structure, the form and arrangement of the glands being very like that seen in the normal mucous membrane.

The striking similarity which exists between blastomatoid conditions and true blastomata is very clearly shown in the papillomata, for the more we study these tumours, the more obvious does it become that the majority of them are really hyperplastic and reactive processes. In some cases it is a known infection which gives rise to the papillomatous proliferation of the affected cells ; in others we can with safety deduce an infection from the clinical aspect of the lesion, though the causal agent remains unknown. Or, as in the case of the worker in paraffin, an obvious source of chronic irritation may have been present for a considerable time.

The most striking examples of parasitic papillomata are seen in Coccidiosis of the rabbit and Bilharziasis of man. In the former disease the animal's liver is studded with round whitish tumours which, upon examination, are found to consist of proliferated bile ducts. The tumours have the structure of papillary cystadenomata, but the existing agents, the coccidia, are present in great numbers in the epithelial cells and in the cysts themselves (Fig. 50). In man, the presence of the ova of the bilharzia in the rectum and the bladder gives rise to a papillomatous hyperplasia of the mucosa scarcely to be distinguished from a true blastoma ; moreover, this condition may gradually become carcinomatous.

With regard to the skin, an analysis of the various forms of papilloma which occur suggests that an authentic blastoma of

this type is a rarity. To quote a few of the more striking examples, the multiple warts of childhood are in all probability infective in nature, though we do not know the causal agent; and the same may be said of the venereal warts which form massive papillomata on, and in the neighbourhood of, the genital organs,

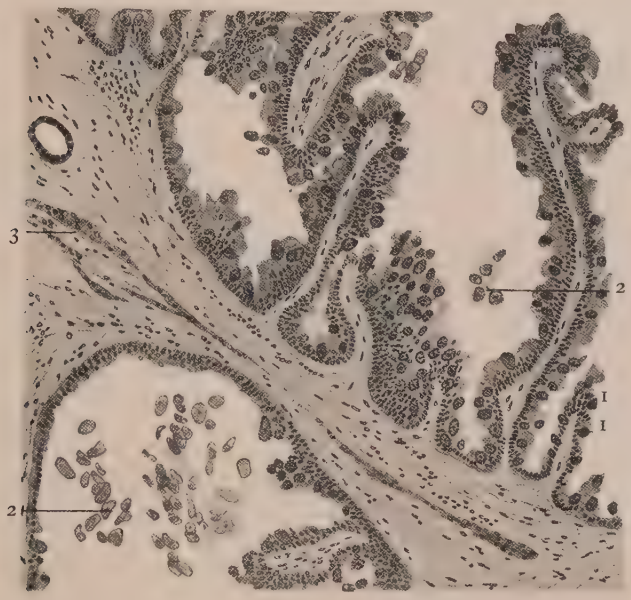

Fig. 50.—Coccidiosis of the rabbit's liver. There is extreme cystic dilatation of the bile ducts with papillomatous ingrowth of the lining membrane. Numerous coccidia can be seen in the epithelial cells (1), and some are lying free in the cysts (2); compressed liver cells (3).

Obj. 8 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

usually in association with a chronic gonorrhœa. Again, molluscum contagiosum is an infective disease of unknown origin. It is characterised by the formation of small umbilicated warts on the skin, especially of the face and head. The histology is distinctive, consisting of a papillomatous overgrowth of the cells of the surface epithelium with a peculiar hyaline degeneration of those of the deeper layers.

Adenoma

The adenomata are innocent tumours, having a slow rate of growth and a sharply-defined margin.

They are composed of epithelial cells which in their size, shape, and general regularity of form approximate very nearly to the normal, and these are arranged in such a manner as to reproduce with a considerable degree of accuracy the structure of the tissues from which they are derived.

Since all the different glandular tissues of the body may be the seat of neoplastic processes, it follows that the adenomata present a very varied structure. It is, however, unnecessary to enter into a detailed description of all the types, and we may content ourselves with a consideration of those characters which are common to these tumours as a whole.

The site of origin influences to some extent the mode of growth of the tumours, and enables us to divide them roughly into two classes, the intraglandular and the polypoid. Thus, the adenomata arising in the substance of a glandular organ are more or less spherical in form and are sharply encapsuled; if, however, they grow in a mucous membrane such as that lining the alimentary canal or the uterus, their shape is somewhat more irregular, and they are nearly always pedunculated.

Again, the structure of the tumour is largely dependent on that of the parent organ. For example, in solid glands such as the liver, the adrenal gland, and the sebaceous glands of the skin, the cells of the tumour will be massed together in trabeculæ or solid alveoli, with little or no attempt at the formation of acini; but in adenomata of tubular or racemose glands, a tubular or acinous arrangement is the rule. This distinction, however, does not always obtain, for acini may be found in tumours of the former group, and in the latter there may be a solid alveolar structure.

Of greater importance is the high degree of differentiation possessed by the cells of adenomata. In the majority of cases they are capable of carrying on their normal functions to a considerable extent, and so we find bile produced in adenomata of the liver, "colloid" in the tumours of the thyroid, and mucin from the goblet cells of the intestinal growths. Where the secretion of mucin or colloid is abundant, the structure of the tumour will be proportionately modified, for the arrangement of

the acini is quite irregular, and there is no provision for the removal of the secreted material such as is provided by the ducts of the normal gland. The acini will become distended with the retained secretion, with the result that the tumour is converted into a collection of cysts, a cystadenoma.

The cells lining the cysts may gradually atrophy from pressure of the contained fluid, or they may remain active and grow into the lumen, giving rise to the papillary cystadenomata with which we are familiar in connection with the breast, the thyroid, and the ovary.

FIG. 51.—Tubular adenoma of the kidney. The tumour consists of irregular elongated tubules, lined by a single layer of epithelial cells.
Obj. 8 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

In the tubular or acinous adenomata (Figs. 51 and 52) the cells naturally vary in shape in different tumours ; in some they are of the high columnar type, in others low or cubical. They are usually arranged in a single layer which rests upon a basement membrane composed of condensed connective tissue, but quite commonly they may be two or three layers deep. In spite of statements to the contrary, it is important to realise that such a multiplicity of cells lining the acinus is not necessarily a sign of malignancy, but is quite a common feature in innocent tumours.

Reference has already been made to compound epithelial and connective tissue tumours, in which both tissues play an equally important part. The most characteristic examples of this group are to be found in the ***fibro-adenomata*** of the breast,

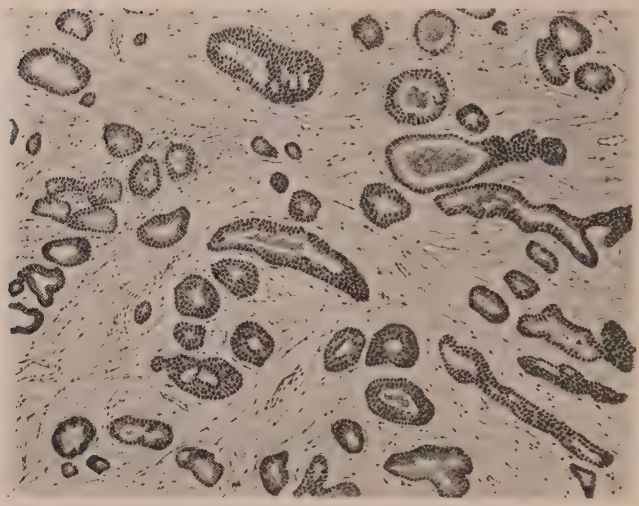

FIG. 52.—Adenoma of the breast. The epithelial tubules are irregular in shape, and are often lined by two or more layers of epithelial cells. The stroma is dense and abundant.

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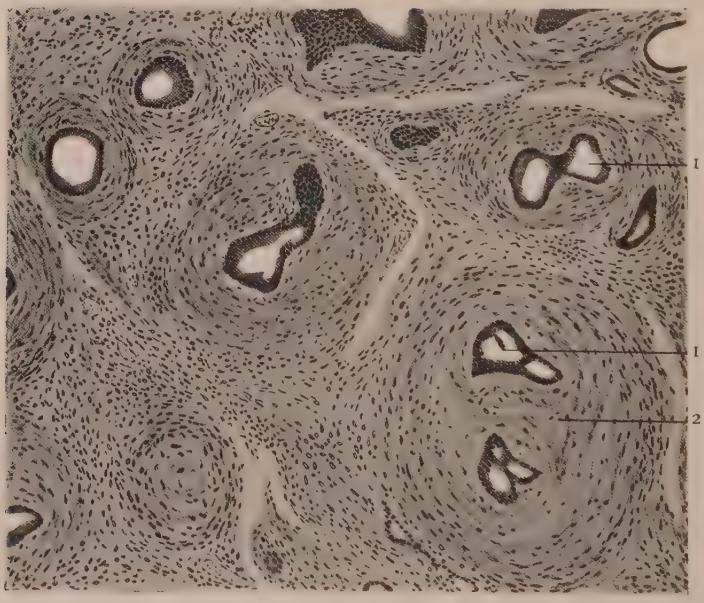

FIG. 53.—Pericanalicular fibro-adenoma of the breast. The breast acini (1) show little change, but the fibrous tissue is increased in amount and is highly cellular; it forms a particularly dense sheath around the acini (2).

Obj. 16 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

where, associated with a hyperplasia of the glandular elements, there is a progressive growth of the fibrous tissue. Two main types exist. In the first, the ***pericanalicular fibro-adenoma*** (Fig. 53), the fibrous tissue growth is chiefly marked around the gland acini which themselves show a pronounced hyperplasia. In the second, the ***intracanalicular fibro-adenoma*** (Fig. 54), the tubules become stretched and drawn out by the general

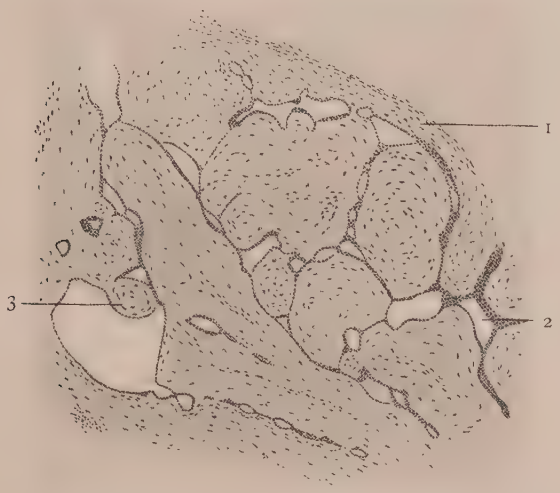

Fig. 54.—Intracanalicular fibro-adenoma of the breast. There is a diffuse hyperplasia of the fibrous tissue (1), and the acini are elongated and distorted (2), and filled by ingrowths of the fibrous tissue (3).
Obj. 16 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

overgrowth of the fibrous tissue. There is a tendency to the formation of cysts which become occupied by projections or ingrowths of the connective tissue.

Only rarely do these tumours seem to be in reality compound growths; usually either the fibrous tissue or the epithelium is the seat of the original progressive change, and in the majority of cases it is the fibrous tissue, so that it would be more correct to describe them as adenofibromata.

Progressive overgrowths of epithelium of a blastomatoid nature are numerous and difficult to distinguish from true blastomas. Some are apparently the result of some form of chronic irritation, in others the cause is more obscure. In the liver and the thyroid gland it is almost impossible in many cases

to differentiate between simple regenerative processes, irritative hyperplasias, and blastomas; and similar difficulties are met with in respect to the breast and the prostate. While it is unnecessary to labour the point, or to multiply examples, it must be remembered that the nature of a "tumour" composed of epithelial cells may be quite as obscure as a similar growth in the connective tissues.

THE CARCINOMATA

In many respects this group is the most important of all those we have to study. It is important numerically, for a considerable proportion of all the neoplasms of any clinical significance belong to it; and its members, by virtue of their distinctive structure, afford unrivalled facilities for the general study of the origin, growth, and spread of tumours.

The carcinomata are malignant epithelial tumours, bearing the same relationship to the innocent epithelial tumours as do the sarcomata to the innocent connective tissue growths.

They are, therefore, cytomata, and are composed essentially of epithelial cells which are not arranged so as to form tissues.

But, as in the sarcomata, malignant tumours occur in which we can distinguish the formation of an atypical issue, so in the carcinomata the cells may be grouped together to form a recognisable lining epithelium or gland tubules. Occasionally the resemblance to the normal tissue is so close that there may be considerable difficulty even in deciding whether a given tumour should be classed among the adenomata or the carcinomata, and this not only in those intermediate or borderline tumours which, naturally, we should be prepared to meet with from time to time, but also in growths having a very definite degree of malignancy.

Nevertheless, the rule holds good in the majority of cases, and whereas the adenomata mimic with some exactitude the tissue from which they are derived, though the structure of the organ is not reproduced, the carcinomata are composed of epithelial cells which rarely form more than the imperfect rudiments of a tissue.

Although in the majority of carcinomata the cells of the tumour are obviously of the epithelial type, this is not always so, and it is necessary to keep in mind the fact that anaplasia

is one of the most striking characteristics of the malignant cell. The more malignant a tumour is, the more will its elements deviate from the normal and revert to the embryonic type ; and although the cells certainly retain their lepidic characters in being in absolute apposition with one another, it is only by the study of a series of tumours of varying malignancy that we can trace the connection between normal lining or glandular epithelium and the more undifferentiated carcinomata.

The naked-eye appearances of the carcinomata are extremely variable. It is usual to describe three main forms, the ulcerative, the nodular, and the fungating ; but in the finer details no two tumours are exactly alike, and even the grosser features depend very largely upon factors of quite secondary importance.

The colour is usually white or grey, and the consistence is harder than that of the surrounding tissues.

The cut surface may be mottled yellow or red from fatty degeneration or hæmorrhage, while mucoid degeneration will give a translucent " colloid " appearance.

The presence of a stroma makes the carcinomata seem to have a more organised structure than the sarcomata, and helps considerably in the differential diagnosis between the two growths.

Much of what it is necessary to say concerning the general properties of the carcinomata, their origin, growth, and dissemination, will be found in preceding chapters ; we need consider now only some of their more particular features.

The structure of a carcinoma is very much more complicated than that of a sarcoma, for it consists not only of the essential epithelial cells of the growth, but also of the blood vessels and connective tissues which nourish and support them. And though the connective tissue element appears to be of secondary importance, it plays a very necessary part in the life of the tumour. If, from one cause or another, the blood supply is inadequate, the tumour cells will die ; if, as may sometimes be seen in small malignant emboli in blood vessels, the connective tissues fail to supply a supporting scaffolding, the cells are unable to survive ; or if the connective tissue reaction is excessive, the parenchymatous elements may be partly or entirely choked and killed.

It is not out of place, therefore, to enquire a little more closely than we have hitherto done into the nature and origin of this stroma.

A carcinoma may increase in bulk in two ways: it may infiltrate the surrounding healthy tissues, destroying the specific cells of the part and utilising as a stroma the existing connective tissues; or it may exhibit a combined growth of its cells and stroma, quite apart from any addition to its mass by the absorption of surrounding structures.

While the former mode of progression is characteristic of the carcinomata, as it is of all malignant growths, and is of much greater clinical importance, it is easy to demonstrate that both are active simultaneously, though not necessarily to the same extent.

If we examine secondary carcinomatous nodules in an organ such as the liver, we are struck by the fact that the superficial metastases project only slightly above the surface, though they extend for some distance into the substance of the organ. In other words, the growth of the tumour is mainly at the expense of the pre-existing tissues.

Nevertheless, there is a certain amount of independent growth on the part of the tumours, for they often are raised to some extent above the surface, and their deeper margins are fairly sharply defined; moreover, a microscopical examination shows nearly always some compression of the liver cells at the periphery of the nodule, distinct evidence of an expansive growth.

But it is only in the more slowly growing forms that independent or expansive growth is at all marked. With a higher degree of malignancy the great mass of the tumour results from the invasion and destruction of the adjacent structures; indeed, we find the stroma in the central parts lagging behind the more active parenchyma, which, deprived of the necessary nourishment, dies. It is to the central death of the cells, with the subsequent slow replacement by fibrous tissue, that the umbilication of superficial tumours, an important sign in the differential diagnosis between neoplasms and inflammatory formations such as gummata, is due.

Whatever its origin may be, whether intrinsic or extrinsic, we find the stroma varying considerably in character in different classes of tumours.

Its composition is always quite simple, consisting only of fibrous connective tissue and blood vessels; but the amount of formed fibrous tissue, the number and activity of the fibroblasts, and the richness of the vascular supply all differ within very wide limits.

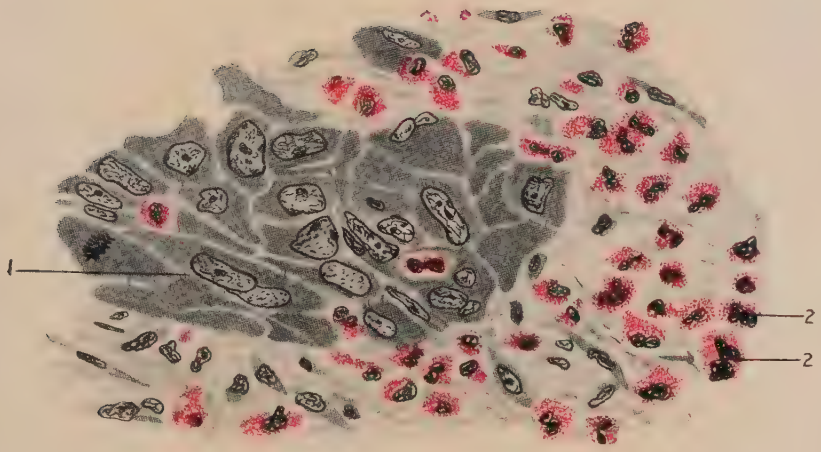

Fig. 55.—Microscopic section of a squamous-celled carcinoma of the pharynx, showing dense eosinophile-celled infiltration of the stroma. (1) Carcinoma cells (one in mitosis); (2) eosinophile cells.

To face p. 138.

As a rule, we find an abundance of stroma in the carcinomata derived from epithelium which normally possesses a rich connective tissue investment, and *vice versa*. Thus, the breast is an organ containing a large quantity of connective tissue, and carcinomata of the breast have usually a plentiful well-formed stroma. Again, there is little supporting tissue in the normal liver, and primary liver-cell carcinomata have but a scanty stroma; but bile-duct carcinomata are of a more scirrhous type, for the hepatic bile ducts are enclosed in a distinct fibrous tissue sheath. The rule, however, is only of general application; many other factors, of which the most important is the rate of growth, combine to modify it. Where growth is slow the stroma is dense and abundant; in the more rapidly progressing tumours the stroma becomes less and less marked, till in some cases the groups of cancer cells are supported by nothing stronger than delicate capillary blood vessels.

The activity of the fibroblasts is influenced very strongly by the tumour cells, and sometimes the stroma may be excessively cellular. Frequently also there are present numbers of adventitial cells; these are for the most part contained in the stroma, but they may penetrate into the parenchyma, insinuating themselves among the tumour cells. They are chiefly seen at the advancing margin of the growth, and are particularly evident on the deep surface of tumours derived from the surface epithelium.

This ***round-celled infiltration*** consists almost entirely of lymphocytes and plasma cells, though a few eosinophile cells are sometimes to be seen, and an occasional mast cell.

It appears to be in the nature of a reaction against the growth, but it is by no means constant in its presence. The source of the cells is somewhat obscure. With the possible exception of the mast cells none of them are native to the tissue, but it is still uncertain whether they are brought to it by the blood stream or by the lymphatics; there is at any rate no comparable change in the blood picture.

Should the tumour become ulcerated there is usually an active determination of polymorphonuclear leucocytes to the part, and this may be accompanied by so strong a reaction on the part of the stroma as to obscure almost completely the character of the growth.

Apart from ulceration, polymorphonuclear leucocytes occur but rarely in carcinomata.

I have already drawn attention to the presence of occasional eosinophile cells in the zone of small round-celled infiltration.

Although they are seldom a prominent feature, tumours are sometimes encountered where they are present in such enormous numbers as to dominate the histological picture (Fig. 55). In my own experience, this occurs only in squamous carcinomata, though I have seen it in several different varieties of this type of tumour, in carcinomata of the cervix uteri, the lip, the tongue, and the pharynx. It is doubtful what significance should be placed on this phenomenon, but it is certainly more than a purely local effect, for it is accompanied by a pronounced eosinophilia of the circulating blood which disappears should the tumour be extirpated.

The only other constituent of the stroma to be mentioned is the giant cell. This is of the " foreign body " type, and is seen almost exclusively in the more chronic squamous carcinomata. In these tumours giant cells may be present in considerable numbers in the neighbourhood of the larger masses of keratin, where they play the part of phagocytes or scavengers of the dead tissue.

Turning now to a detailed study of the various types of carcinoma, we find ourselves confronted with a great mass of tumours, derived from all the epithelial tissues of the body, and exhibiting correspondingly wide variations in gross and minute structure.

It is obviously necessary, therefore, to adopt some scheme of grouping in order to simplify our task ; but this is not very easy to do.

There are of course three main sources of origin to any one of which a carcinoma may be traced : (*a*) the lining or glandular epithelia ; (*b*) the cells of innocent epithelial tumours, adenomata, and papillomata ; and (*c*) epithelial rests ; and it might be possible to model a classification on these lines. There are, however, obvious difficulties in this course. It implies an ability to distinguish in every case the derivation of the cancer cell from its morphology, which we are far from possessing ; it assumes that all tumours of any particular epithelium are similar in their structure, which is not true ; and it depends upon theories which have not yet received universal acceptance.

The gross structure and biological properties of the tumours are too variable to permit of their being used as standards ; and

we are therefore reduced to a system of grouping based upon a recognition of the two great varieties of epithelium, lining or protective, and glandular, and the microscopical features of the cancer cell.

In the course of time many different descriptive terms have been applied to the carcinomata; some have become obsolete, but others have much to recommend them and have passed into general use. But since they are not invariably employed to express the same idea, it is necessary to define the meanings which should be attached to them.

In this country the name ***epithelioma*** is applied to a carcinoma of the squamous epithelium such as that covering the skin or the tongue, but on the Continent, and especially in France, it is used for any tumour derived from epithelium. This is obviously more logical; but it would be even more satisfactory to discard the term altogether, for we have already one word to express a malignant tumour derived from epithelium, and squamous-celled carcinoma is a better name for the particular type of tumour in question.

An ***adenocarcinoma*** is a tumour whose cells exhibit in a varying degree an adenomatous or glandular arrangement; the name does not imply in any way that the tumour is derived from an adenoma, or even from a secreting glandular tissue. Similarly, a ***malignant adenoma*** is simply a carcinoma whose structure very closely resembles that of a normal gland.

The term ***duct carcinoma*** is one which might well be discarded. It is applied to tumours arising in the ducts of secreting glands; but such neoplasms have no distinctive features which single them out from any other type of gland carcinoma, and there is no justification for bringing them into a class by themselves.

The terms ***scirrhous***, ***medullary*** or ***encephaloid***, and ***colloid*** applied to a carcinoma indicate that the tumour possesses in a high degree a particular characteristic, an excess or a deficiency of stroma, or an extreme tendency to mucoid degeneration. Used in this way the terms are helpful, but it is quite incorrect to use them as indicative of a distinct class of tumours, for the feature in question may be entirely local. Thus, a carcinoma of the breast may be extremely dense and scirrhous in the central parts from excess of stroma (Fig. 56), but towards the periphery the proportion of cells to stroma may increase considerably, and the

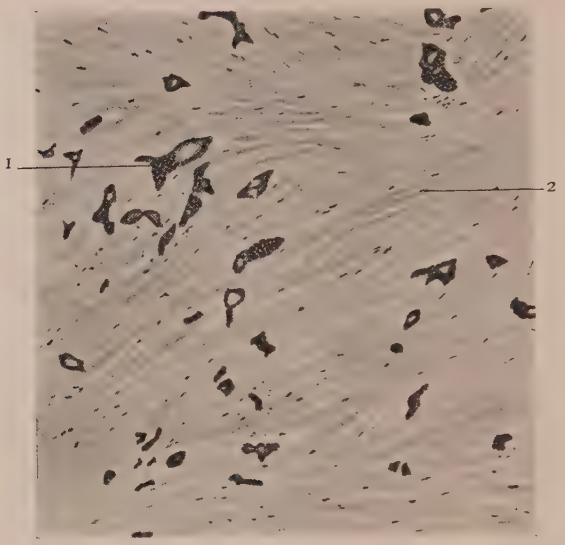

Fig. 56.—Scirrhous carcinoma of the breast. The groups of cancer cells (1) are compressed and separated from one another by an abundance of dense fibrous tissue (2).

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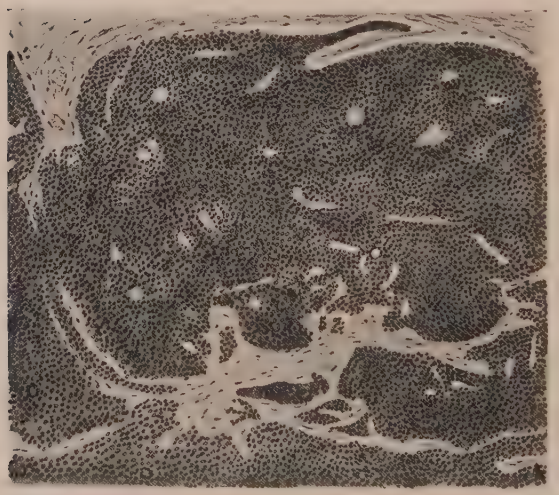

Fig. 57.—Microscopic section of an axillary lymphatic gland showing secondary growth in the form of a medullary carcinoma. Secondary to the carcinoma of the breast from which Fig. 45 was drawn.

Obj. 16 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

metastases may contain the smallest amount of connective tissue and be soft and brain-like (Fig. 57), justifying the name encephaloid or medullary. Certainly the tumour cells control to a great extent the amount of stroma which surrounds them, but a cancer growing in and infiltrating an already hard and mastitic breast may only be a scirrhous growth by the accident of the nature of the soil in which it is growing.

Again, colloid carcinomata do not always exhibit in every part a similar degree of mucoid degeneration, nor is the condition always present in tumours of any particular type of epithelium.

A. Carcinomata of Lining or Protective Epithelium

The tumours of this group arise from the skin, the mouth, the pharynx, the œsophagus, the lining of the pelvis of the kidney, the ureter, the bladder, the vagina, and cervix uteri. These are all situations invested by stratified or transitional epithelium, and the tumours are all classed together as squamous-celled carcinomata, though they exhibit marked differences according to whether they originate in a complicated structure like the epidermis, or in a simpler epithelium such as that lining the bladder.

The histological features of a typical squamous-celled carcinoma of the skin are extremely characteristic. The tumour consists of broad branching columns or large solid masses of cells which include representatives of the various elements present in the parent epithelium. Thus, in the larger masses the peripheral cells are smaller than the central ones, they stain more deeply, and are joined together by a system of delicate protoplasmic bridges to which the name " prickle cell " is due. The central or older cells tend to exhibit degenerative changes similar to those seen in the normal epithelium. They become larger and clearer, and some of them are loaded with granules of eleidin. Finally, in the oldest cells of all, degeneration is complete, and the interior of the mass is occupied by keratinised or horny cells which form the " cell-nests," or " epithelial pearls " that are usually regarded as being the distinguishing mark of the squamous-celled carcinoma (Figs. 58 and 59).

These, then, are the diagnostic features of this variety of tumour: the presence of prickle cells, of cells containing eleidin granules, and of keratinisation. But it must be remembered that they are only pronounced in comparatively slow-growing

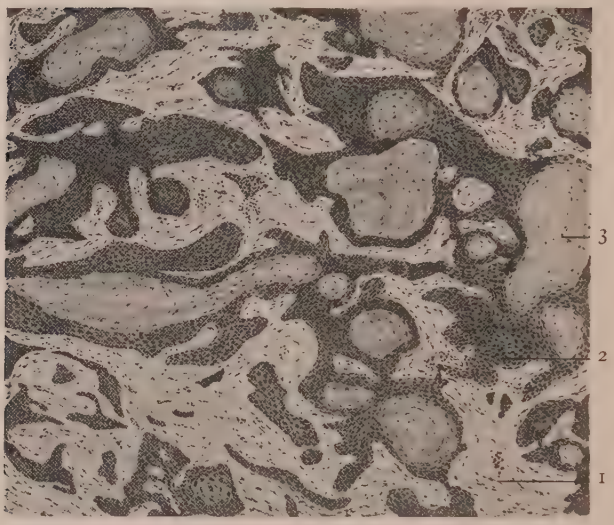

FIG. 58.—Squamous-celled carcinoma of the cheek. (1) Stroma; (2) massive columns of epithelial cells showing (3) keratinisation and cell nest formation.
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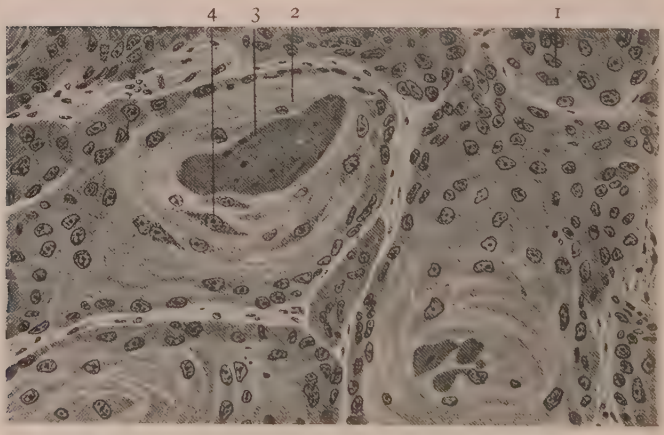

FIG. 59.—Microscopic section of a squamous-celled carcinoma of the tongue. (1) Prickle cells; (2) clear cells corresponding to stratum lucidum; (3) central masses of keratinised cells; (4) cells containing eleidin granules and representing cells of stratum granulosum.
Obj. 8 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

tumours ; with a greater rapidity of growth they may be modified very considerably.

In the first place, it is quite common to see a tumour which exhibits no granular cells at all, and although keratinisation is seldom absent altogether, it may be only rudimentary in the greater part of the growth. Again, the intercellular bridges may be absent or imperfectly formed, so that true prickle cells are present in very small numbers. Therefore, although from a

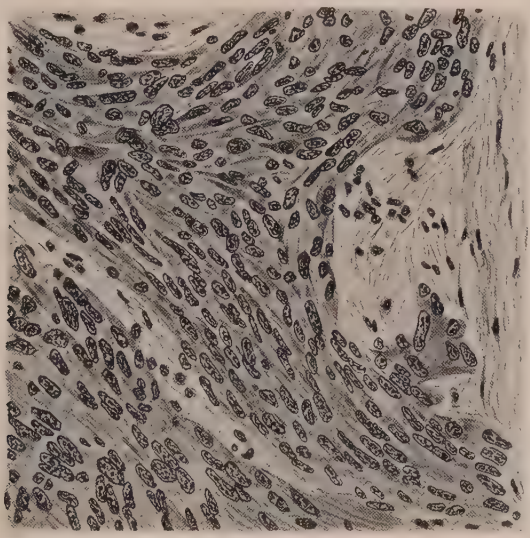

Fig. 60.—Microscopic section of squamous-celled carcinoma of the pharynx, showing spindle-celled appearance of the epithelial cells. In other parts of the section quite typical " cell-nests " are formed.
Obj. 16 mm. apochrom. Comp. oc. 18. Tube length, 160 mm.

general consideration of the shape, size, and arrangement of the cells we may have no doubt as to the real nature of a tumour, an absolute proof may be difficult to establish.

This is particularly so in the tumours of the œsophagus and pharynx. In the antrum of Highmore, also, there occurs a squamous carcinoma which may be extremely atypical.

Even in the more characteristic growths of the skin and the tongue we may meet with unusual appearances in association with a high degree of malignancy. The common rounded type of cell may be replaced by one in which the cytoplasm is drawn out and compressed into a spindle, and areas of the tumour may bear a striking resemblance to a spindle-celled sarcoma (Fig. 60).

Or the cells may become polygonal in shape, and assume a trabecular arrangement ; this is seen in rapidly growing tumours infiltrating a tissue such as muscle (Fig. 61). Apart from these extreme deviations from the usual, it is not uncommon to find very marked differences in the size and shape of the cells. Large multinucleated forms may be seen, and various kinds of cell inclusions are quite numerous.

Besides the common squamous-celled carcinoma or "epithelioma," there is another interesting type of tumour derived from the skin. It is known in this country as the ***rodent ulcer,***

FIG. 61.—Section of a squamous-celled carcinoma of the tongue invading muscle. (1) Columns of carcinoma cells growing in long trabeculæ among (2) striated muscle fibres.

but on the Continent it is more often termed the ***basal-celled carcinoma,*** in the belief that it grows from the basal cells of the epidermis. This tumour is comparatively innocent, for although its growth is infiltrative, it scarcely ever forms metastases. It is composed of large solid masses of cells of an oval or even spindle shape, which are entirely devoid of prickles, and never become keratinised. It is also quite characteristic for the external layer of cells to be distinctly columnar in shape (Fig. 62).

There is considerable doubt as to the origin of these tumours. The generally accepted view is that they are derived from the hair follicles, but some authorities would trace them to the

sweat or sebaceous glands, while by others they are thought to be really endothelial in nature.

While it is undoubtedly desirable to recognise the rodent ulcers as a distinct class of epidermal carcinomata, since they differ very plainly both histologically and clinically from the squamous-celled carcinomata, there seems to the writer to be a tendency to lay undue stress on this distinction. For tumours presenting very anomalous features are occasionally met with; in parts they show the typical histology of a rodent ulcer, but elsewhere

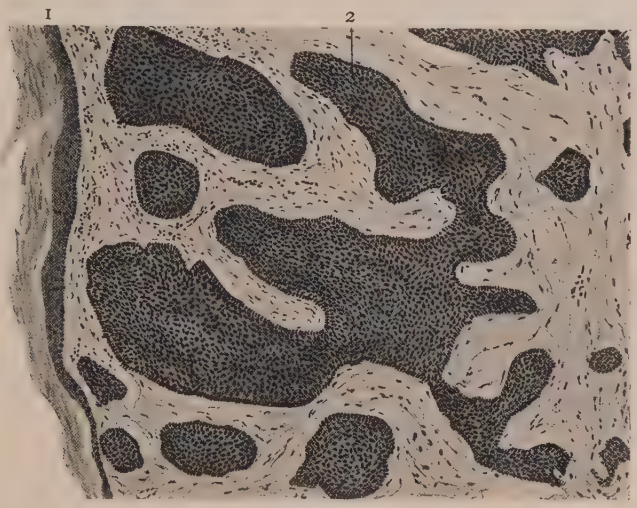

FIG. 62.—Microscopic section of a rodent ulcer. (1) Surface epithelium; (2) massive branching columns of epithelial cells.
Obj. 16 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

they resemble very much more a squamous-celled carcinoma. If we regard the rodent ulcers as being derived from the basal layer of the epidermis, we cannot deny to their parent cells the potentialities of ordinary squamous epithelial cells, including the power of being able to give rise to a squamous-celled carcinoma; and if we refer their origin to the hair follicles, we are dealing with cells of but a slightly higher degree of differentiation.

With regard to the carcinomata of the simpler epithelial membranes, we find that they have a much less complicated structure. A carcinoma of the urinary bladder, for example, is composed of large islands of cells of the transitional or stratified

type, but prickle cells are absent, and there is very rarely any distinct horny degeneration (Figs. 63 and 64).

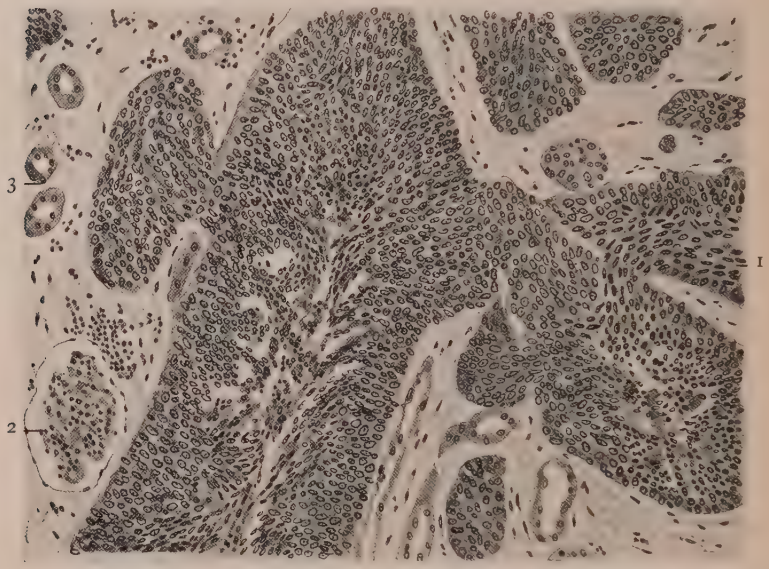

Fig. 63.—Transitional-celled carcinoma of the renal pelvis invading the kidney. (1) Broad columns of malignant epithelial cells; (2) glomerulus; (3) renal tubules. Obj. 8 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

The metaplastic potentialities of epithelial cells are very clearly revealed in the squamous-celled, or mixed squamous-celled and glandular carcinomata occurring in regions lined by columnar epithelium (Fig. 65). Such tumours are rare, but they have been found in several situations, notably in the gall-bladder and the uterus. Their origin has been the subject of much debate, but it is now generally agreed that they are genuine instances of metaplasia, or alteration in type, of the columnar epithelial cells of the organ concerned. In these tumours the change is from columnar to squamous epithelium ; the possibility of the reverse change taking place has not received universal acceptance. One occasionally has the opportunity of examining a squamous-celled carcinoma in which definite acini, lined by a single layer of cubical cells, are present. But there is always the possibility of the tumour being a primary glandular carcinoma—maybe, a sweat gland carcinoma—with secondary metaplasia to squamous epithelium.

FIG. 64.—Microscopic section of a transitional-celled carcinoma of the urinary bladder. Obj. 16 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

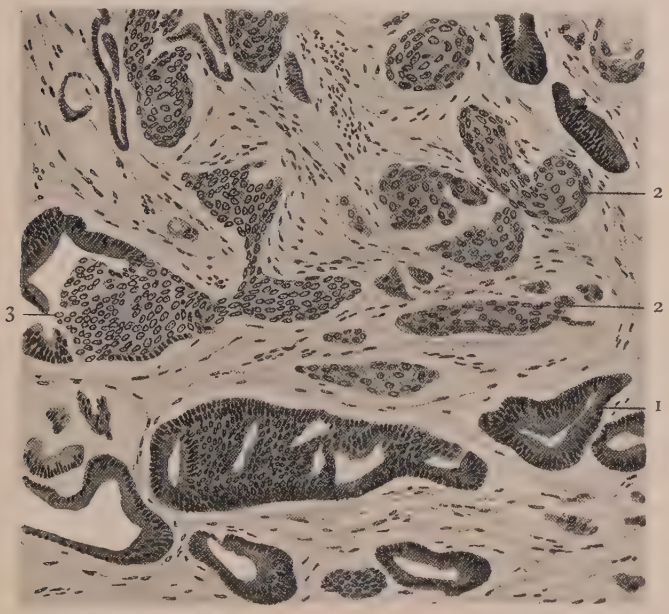

FIG. 65.—Microscopic section of a mixed carcinoma of the common bile duct. The greater part of the growth had the structure of a squamous-celled carcinoma, but the part illustrated shows: (1) Columnar epithelial cells arranged in irregular acini; (2) masses of squamous epithelium; (3) acinus showing transformation of columnar to squamous epithelium.

Obj. 16 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

The question is probably impossible of solution by the study of the tumours as they appear in the human subject, but it has been worked out with great completeness in the case of the mouse (p. 53).

B. Carcinomata of Glandular Epithelium

This group may be subdivided into two according to the degree of differentiation of the tumour cells :

(*a*) Carcinoma simplex : composed of polygonal or spheroidal cells, destitute of any glandular arrangement.

Fig. 66.—Microscopic section of a carcinoma simplex of the breast. The tumour consists of undifferentiated epithelial cells arranged in alveoli or branching columns. There is a moderate amount of fibrous stroma.
Obj. 16 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

(*b*) Glandular carcinomata : composed of columnar or cubical cells arranged in acini or tubules, or in such a manner as to recall the structure of the parent gland. They are known under a variety of names : adenocarcinoma, columnar-celled carcinoma, duct carcinoma, and malignant adenoma.

(*a*) **Carcinoma Simplex.**—This tumour is seen to perfection in the mammary gland, but is by no means peculiar to this organ, for in many other situations carcinomata may grow whose cells show an equal lack of differentiation.

The cells of the growth are more or less spheroidal in shape, hence the name " spheroidal-celled carcinoma " by which they

are often known; but they are very commonly distorted by mutual pressure into an irregular polygonal form. They have a fairly abundant granular cytoplasm, and a nucleus rich in chromatin. Inequalities in size and shape of both cells and nuclei are not uncommon, and cell inclusions may frequently be observed.

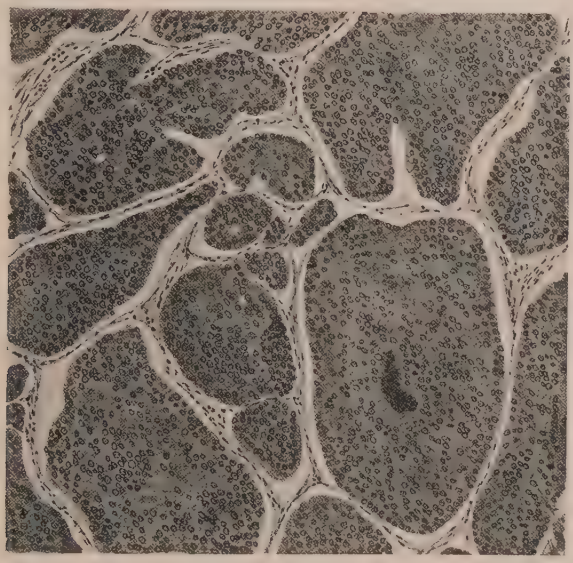

FIG. 67.—Section of a carcinoma simplex of the breast of the "encephaloid" type. The cells are arranged in large alveoli, and there is only a scanty connective tissue stroma.

Obj. 16 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

The cells are grouped together in solid alveoli or columns of varying width, and are supported by a connective tissue stroma which may be dense and abundant, or delicate and sparse (Fig. 66). In some tumours the alveoli may be extremely large, and separated by only the scantiest connective tissue framework (Fig. 67); in others the stroma is increased out of all proportion to the cancer cells, which are compressed into narrow strands. In the former class there is often evidence of great activity, karyokinetic figures may be numerous, while in the centre of the alveoli the nuclei are often fragmented and degenerated; in the latter the cells have distinctly a more quiescent appearance.

Since these structural differences reflect with some accuracy

the degree of malignancy of the tumours, there is justification for distinguishing the two types by the names "encephaloid" and "scirrhous." But it must be remembered that the proportion of connective tissue to epithelium is not always constant in the same growth; an encephaloid tumour practically always remains cellular, but a scirrhous growth may at any time show a diminution in the amount of stroma, with increased activity of the epithelium. Further, it must be emphasised that a

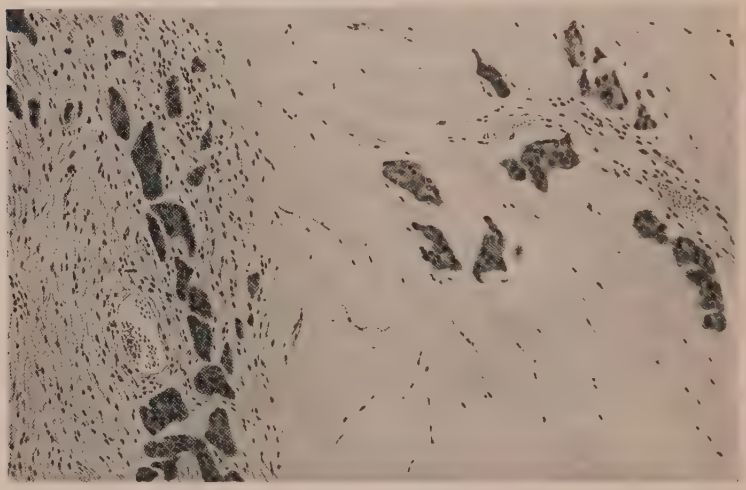

FIG. 68.—Microscopic section of a scirrhous carcinoma of the rectum. The tumour cells show no differentiation, and the stroma is very abundant. On the right-hand side of the figure the fibrous tissue is extremely dense and acellular.
Obj. 16 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

"scirrhous cancer" is not necessarily a carcinoma simplex; a superabundance of stroma may be seen also in the glandular and squamous-celled carcinomata (Fig. 68).

It is reasonable to assume in the life history of a tumour that its cells may alter from time to time in their character; at one period they may be "indifferent," at another they may attain to a higher degree of differentiation. At any rate, we may often notice a transition, gradual or abrupt, to an adenomatous structure in the carcinoma simplex, both in the primary growth and in the metastases.

(*b*) **Glandular Carcinoma.**—This group has a wide distribution, and the individual members naturally have a varied structure.

The form and arrangement assumed by the cells is influenced to some extent by the characters of the parent epithelium, but even more by the degree of malignancy they possess. Generally speaking, the more malignant a tumour is, the more " indifferent " are its cells, though a slowly growing scirrhous carcinoma may show little evidence of a glandular origin.

Fig. 69.—Microscopic section of a malignant adenoma of the rectum. The tumour cells possess a high degree of differentiation, and their form and arrangement indicate their glandular origin.

Obj. 16 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

We can distinguish, therefore, all forms between the malignant adenoma in which the glandular structure of the parent epithelium is almost perfectly reproduced, and the more anaplastic adenocarcinoma which gradually passes into the carcinoma simplex (Figs. 69-73).

The cells may be columnar or cubical, and are commonly irregular both in shape and size. The nuclei are relatively large, but the cell bodies are smaller and denser than normal, especially in the columnar-celled forms.

The acini or tubules are never quite regular, and often vary very much in size and outline. They may be lined by a single

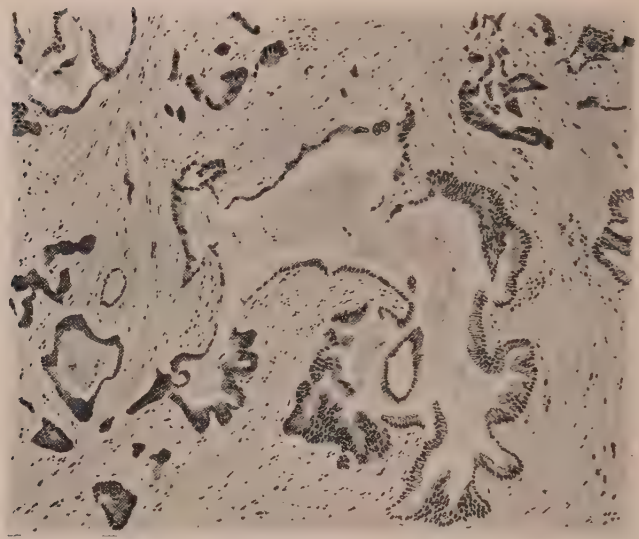

FIG. 70.—Section of an adenocarcinoma of the gall bladder. The tumour cells are very irregular in their form and arrangement.
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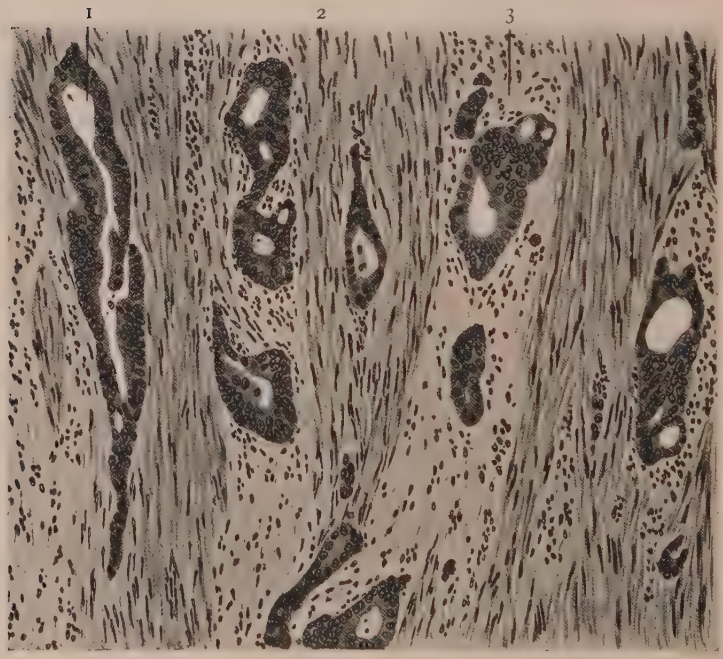

FIG. 71.—Microscopic section of an adenocarcinoma of the stomach, showing tumour acini (1) invading the muscle (2) and connective tissue (3) of the stomach wall.
Obj. 8 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

FIG. 72.—Section of a columnar-celled adenocarcinoma of the breast.
Obj. 8 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

FIG. 73.—Section of an adenocarcinoma of the rectum. The tumour is solid and the cells are not highly differentiated, but every now and then there is a suggestion of an acinous formation.
Obj. 8 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

row of cells, or the cells may be heaped up into two or more layers. Occasionally the acini are dilated into microscopic cysts, and these may become filled by a papillary ingrowth of the lining cells, forming the ***malignant papillary cystadenoma*** (Fig. 74).

Columnar-celled carcinomata often contain mucus-secreting goblet cells; but this is not always so, and some intestinal carcinomata may be entirely devoid of such secretion. Similarly, carcinomata of the liver and the thyroid gland may or may not contain bile or colloid material respectively.

FIG. 74.—Microscopic section of a malignant papillary adenoma of the kidney. The section includes part of two large cysts which are loosely filled with papillary ingrowths of the lining cells. In places there is a slight deposition of calcium salts (I).

Obj. 16 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

Variations in the amount and character of the stroma are seen in different examples of this class of carcinoma, as in the squamous-celled and simple types, in response to influences which have already been indicated.

Retrograde changes are not uncommon in the carcinomata, and are sometimes of considerable importance. They have been treated of in a previous section (p. 14), and it is only necessary to refer to one form, mucoid degeneration. This degeneration is seen in many glandular carcinomata, but in certain cancers of the stomach, the large intestine, and occasionally the breast, it is so advanced that these tumours have been described as a separate class, the colloid carcinomata (Figs. 75-76). Although, no

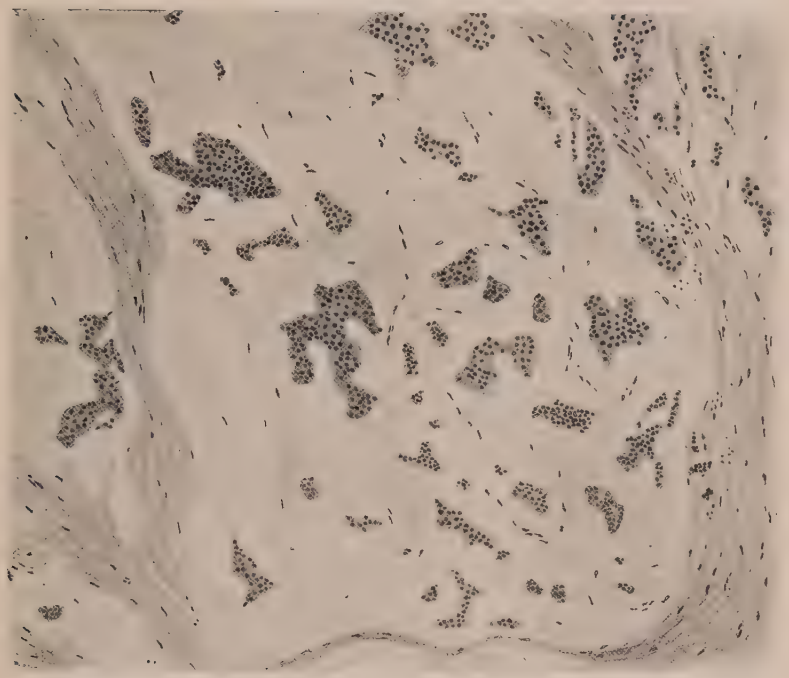

FIG. 75.—Section of a colloid carcinoma of the breast. The tumour cells are grouped together in small alveoli which are surrounded by myxomatous tissue. Broad bands of fibrous tissue traverse the growth at intervals.

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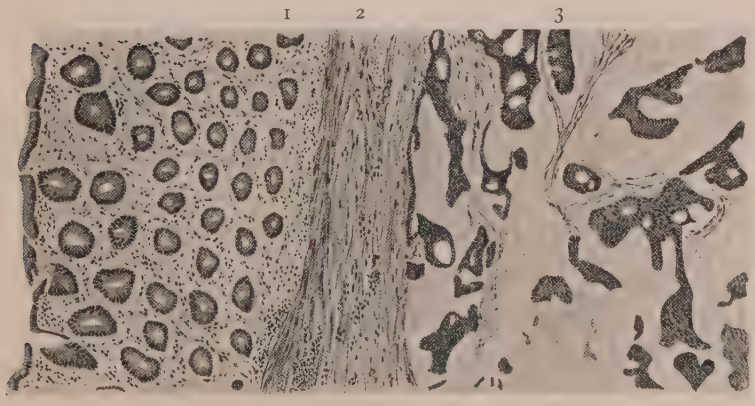

FIG. 76.—Microscopic section of a colloid carcinoma of the cæcum. (1) Normal mucous membrane; (2) muscularis mucosæ; (3) carcinoma acini surrounded by mucoid tissue.

Obj. 16 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

doubt, the name will always be retained, it must be remembered that we are merely recognising an extreme and obvious degenerative change; it would be as logical to class as a distinct entity all tumours exhibiting an unusual degree of fatty degeneration.

Polymorphism in Carcinomata

Although the majority of carcinomata are fairly characteristic in their structure, and can be recognised without much difficulty as epithelial blastomata, from time to time atypical forms are met with in which the tumour cells exhibit a varying degree of polymorphism which may be so extreme as to make the correct classification of the growth a matter of the greatest difficulty.

That the malignant epithelial cell is capable of minor degrees of polymorphism is well recognised. The interchangeability of the acinous and the solid structure in adenocarcinomata is familiar to everyone, as is also the origin of a squamous-celled carcinoma from columnar epithelium, but greater variations than these are not as a rule considered possible. Krompecher,[1] it is true, holds that under certain conditions epithelial cells may actually be converted into connective tissue elements, but his views have not found general acceptance, and the doctrine of the specific nature of cell growth is not seriously questioned. But even if such a degree of metaplasia is impossible, there can be no doubt that certain carcinomata may possess such extreme powers of polymorphic growth that their cells, losing all trace of their epithelial origin, may become indistinguishable from connective tissue cells. The recognition of this power of polymorphic growth is particularly important in the study of the so-called carcino-sarcomata, or "mixed tumours," a few instances of which have been recorded. These tumours are essentially carcinomata in which the stroma has sarcomatous properties, and bear a close resemblance to the mixed tumours which develop in the course of propagation of carcinomata in mice (p. 56). But whereas it is possible by repeated transplantations to analyse the experimental tumours successfully, and to determine exactly what the anomalous histological structure represents, this line of investigation is impossible in human tumours. In them the diagnosis rests entirely on the microscopic examination, and it becomes all the more necessary, therefore, to subject the histological findings to the most careful scrutiny.

[1] Krompecher, *Beitr. path. Anat. u. alle Path.* 1908, xliv. p. 88.

Although it is probable that many of the carcino-sarcomata recorded are true mixed tumours, it is certain that others are merely examples of extreme polymorphism of carcinoma cells.

The possibilities of which the malignant epithelial cell is capable in this direction are illustrated in Figs. 77 to 86.[1]

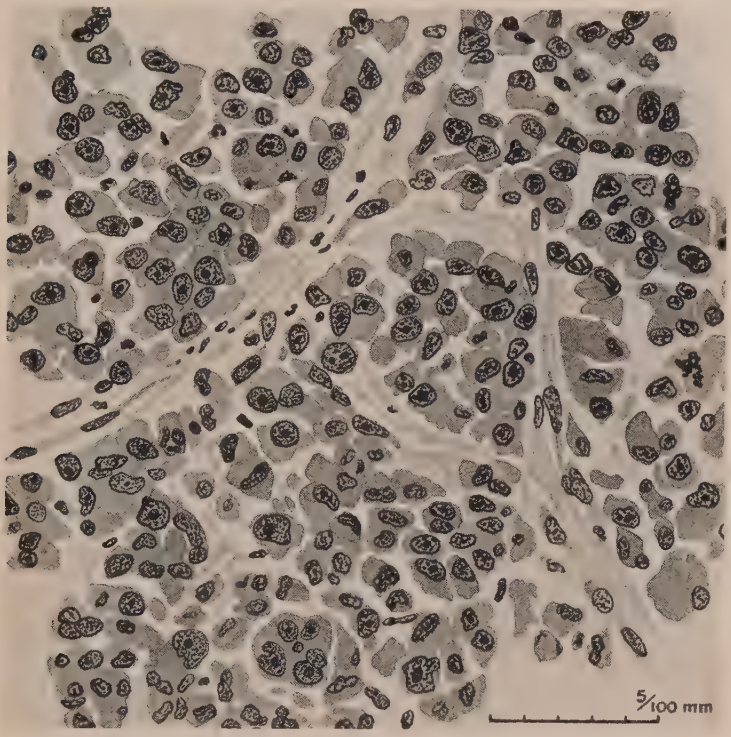

Fig. 77.—Metastasis from a carcinoma of the thyroid. It has the structure of a polymorphic-celled sarcoma and shows no sign of its epithelial origin. Compare Figs. 78 and 79.

Figure 77, drawn from a section of a malignant growth of the thyroid, illustrates the structure of the greater part of the tumour which was originally diagnosed as a polymorphic-celled sarcoma. A more extensive examination, however, revealed the true nature of the tumour. Fig. 78 shows the tumour cells differentiating and forming vesicles which contain "colloid," this structure being combined with a solid alveolar or trabecular type of growth.

[1] See also Kettle, "Polymorphism of the Malignant Epithelial Cell," *Pro. Royal Soc. Med.*, 1914, vol. xii. p. 1.

FIG. 78.—Part of the primary carcinoma of the thyroid illustrated in Figs. 77 and 79. The tumour cells form vesicles which contain colloid. At (1) the cells lose their differentiation and grow as solid trabeculæ.

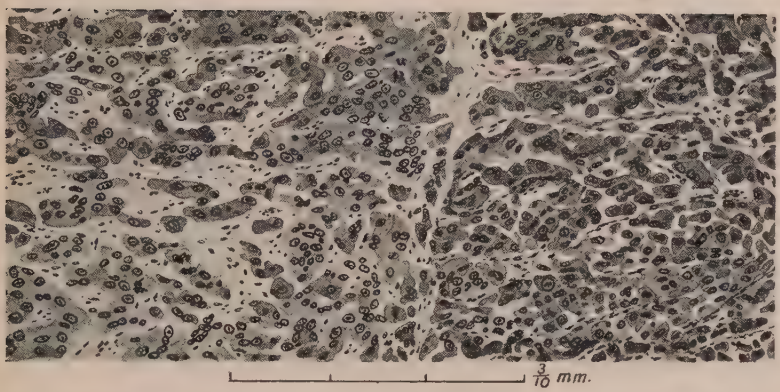

FIG. 79.—A metastasis from the carcinoma of the thyroid illustrated in Figs. 77 and 78. On the left of the figure the carcinoma cells grow as solid trabeculæ. On the right, the cells increase in size, loosen and separate from one another, till the polymorphic-celled sarcomatous appearance illustrated in Fig. 77 is produced.

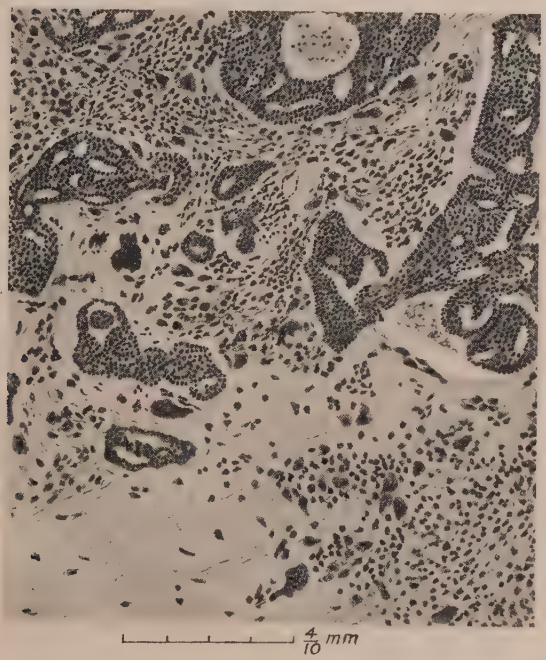

FIG. 80.—An adenocarcinoma of the breast showing a polymorphic giant-celled sarcomatous stroma. Compare with Figs. 81-83.

In Fig. 79, the transition from the solid trabecular to the loose "sarcomatous" type of growth is illustrated. This tumour, then, is not a carcino-sarcoma, but is a carcinoma of the thyroid exhibiting extreme polymorphism.

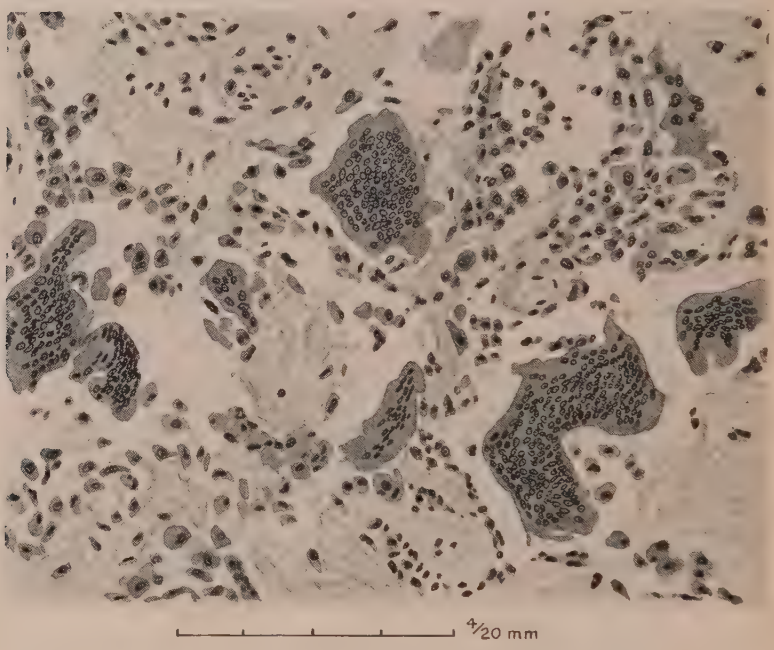

Fig. 81.—High power figure of the stroma of the carcinoma illustrated in Fig. 80.

Fig. 80 illustrates an adenocarcinoma of the breast in which the stroma has the structure of a polymorphic or giant-celled sarcoma (Fig. 81). This stroma, however, really represents atypical growth of the carcinoma cells. Fig. 82 shows the fraying out and loosening of the "stroma" cells from the periphery of carcinoma alveoli; and in Fig. 83 the giant cells are seen to be formed by the fusion of the carcinoma cells with proliferation of their nuclei.

Fig. 84, drawn from a malignant polyp of the uterus, shows the transition of columnar to squamous epithelium, and the cellular, "sarcomatous" stroma. This "stroma," again, really represents the polymorphic growth of the carcinoma cells (Fig. 85).

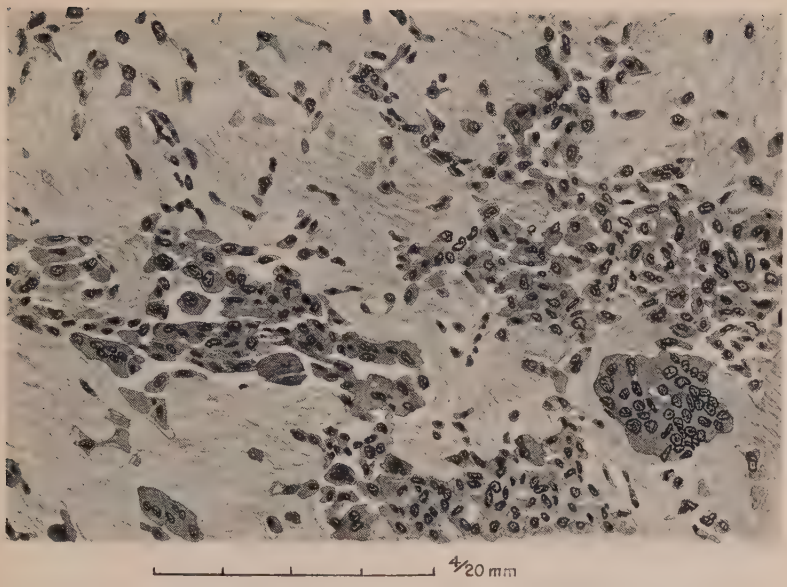

FIG. 82.—Showing the formation of the cellular "sarcomatous" stroma of the tumour (Fig. 80) by the loosening and fraying out of the carcinoma cells.

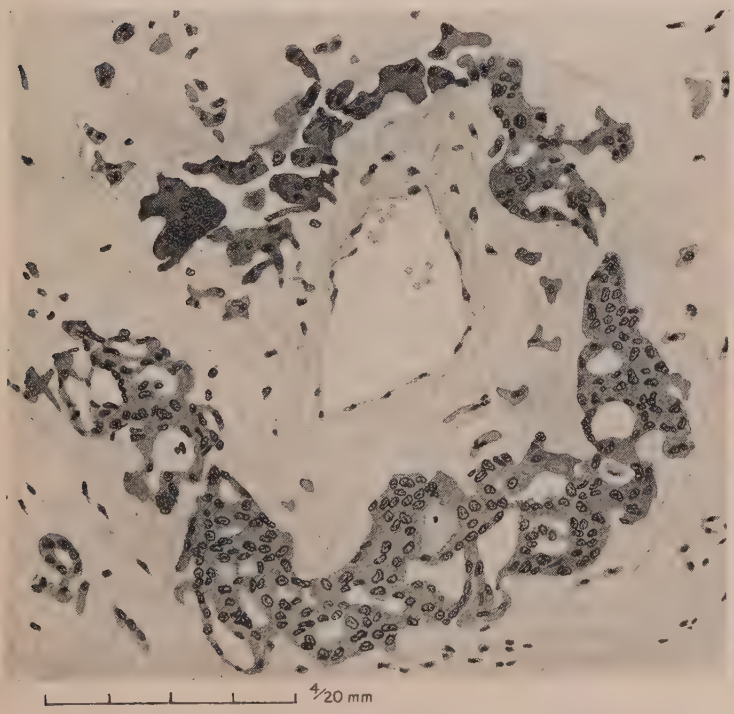

FIG. 83.—Showing the formation of the stroma giant-cells of the tumour (Fig. 80) from the carcinoma cells.

FIG. 84.—Section of an adenocarcinoma of the uterus showing the transformation of the columnar cells (1) to squamous epithelium (2) which keratinises (3). There is a highly cellular spindle- and giant-celled stroma.

Fig. 86 is drawn from a carcinoma of the prostate which disseminated as a pure adenocarcinoma in the iliac glands, and as a mixed adeno-squamous carcinoma in the liver. The figure shows the transition of the adenocarcinoma into the squamous-celled carcinoma, and, in addition, the highly cellular "sarcomatous" stroma. This "stroma" is actually formed by the loose, atypical growth of the squamous-celled elements of the carcinoma.

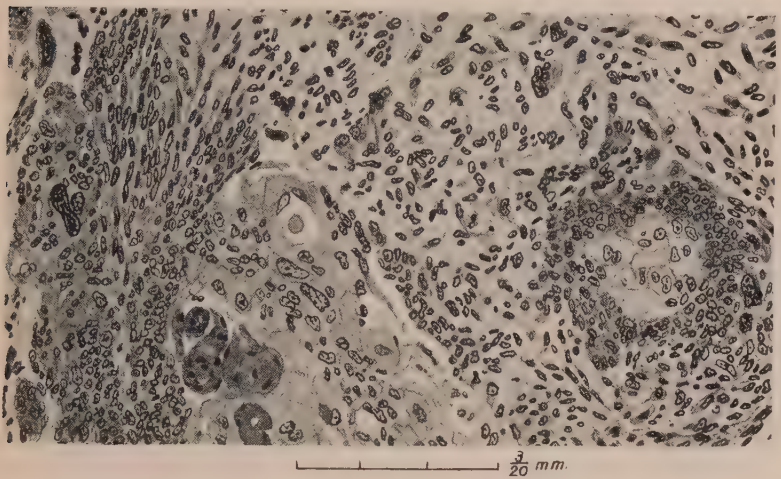

Fig. 85.—Section of the tumour illustrated in Fig. 84 showing the squamous-celled type of growth and the formation of the cellular "sarcomatous" stroma by the fraying out of the carcinoma cells.

These tumours lend themselves fairly readily to histological analysis, and their true nature can be determined with some degree of certainty. Other "mixed tumours," however, are much more difficult, and in them an absolute diagnosis may be impossible.

But, since the neoplastic epithelial cell can exhibit these remarkable powers of polymorphic growth, it is necessary to study any anomalous carcinoma with the greatest care before indulging in a diagnosis of "mixed tumour." Above all is it necessary to exercise restraint in drawing broad conclusions from the study of human material, for microscopy, our only available method of investigation, may woefully mislead us.

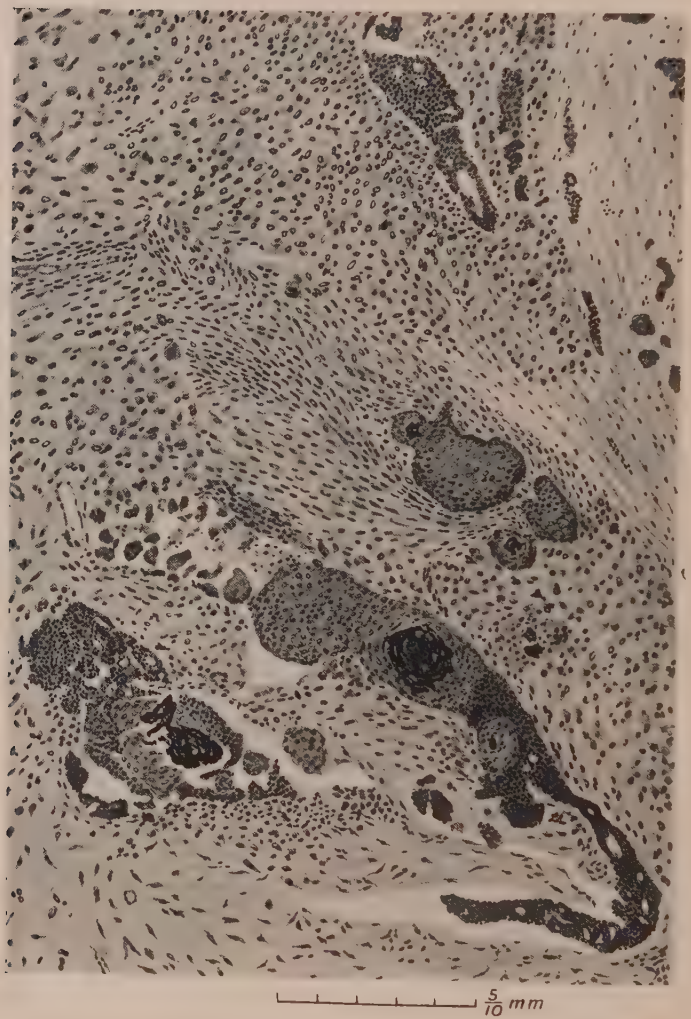

FIG. 86.—A polymorphic-celled carcinoma of the prostate. There is direct transformation of the glandular carcinoma into squamous cells. The stroma is cellular and "sarcomatous," but this appearance is due to the atypical, polymorphic growth of the carcinoma cells.

THE ENDOTHELIOMATA

In entering upon a description of the tumours derived from endothelium we are confronted with quite exceptional difficulties, for in respect to no other class of neoplasms is there so wide a divergence of opinion.

There are some pathologists who make a diagnosis of endothelioma in only the rarest cases, and then more as a concession to existing prejudices than from a sense of conviction; in the view of others the endotheliomata occupy a large and important place, and include many tumours which more conservative observers would describe unhesitatingly as carcinomata. Even among the extremists of the latter school there seems to be some uncertainty exactly as to what constitutes an endothelioma, and there is no authoritative pronouncement on the subject to which the student can refer.

In Adami's system of classification the endotheliomata come under the heading of ***transitional lepidomata***; they are regarded as being developed from "rind" tissues which are themselves derived from the primitive "pulp." In their growth, therefore, they may assume lepidic, or epithelial, characters, or, if of a higher grade of malignancy, they may revert back to the more primitive sarcomatous type of cell. This behaviour on the part of the vegetative endothelial cell necessarily militates against complete uniformity in our interpretations of different histological pictures, and may explain to some extent the confusion that surrounds these tumours; but much of the trouble seems to result from fundamental differences in our conceptions of what constitutes a carcinoma, and of the potentialities and limitations of malignant cells in general.

The innocent endothelial tumours, the histiomata, present few difficulties, and their nature is seldom in doubt. It is in the malignant forms, the cytomata, that confusion arises, because the standards by which the neoplastic endothelial cell can be recognised are not clearly defined.

According to most authorities the points of importance in the diagnosis would seem to be the following: The close relationship of the cells to blood vessels; their whorled arrangement, and the absence of any suggestion of a glandular or acinous formation; the presence of giant cells; the tendency on the part

of groups of cells to form central lumina which often contain blood; the formation of regular columns of cells two or three layers thick, or of elongated tubules; and the comparative innocence of the tumours.

It is necessary to examine certain of these properties closely in order to determine whether they can really be considered distinctive of any particular form of tumour.

Taking first the close relationship of the tumour cells to blood vessels, we find that this occurs in many neoplasms. It is very common in the sarcomata, and may often be seen in the carcinomata; nothing, for example, could be closer than the association between the parenchyma and the supporting capillaries of the hypernephroma. Mere grouping of the cells around vessels, then, cannot be considered a peculiar property of the endotheliomata; it is necessary to demonstrate a much more intimate connection—the direct origin of the cells from endothelium, or an attempt on their part to exercise their normal function of lining channels which could contain circulating blood or lymph. In the ordinary course of events the normal structure of the tissues must be completely obscured by proliferation of the tumour cells, and in growths of any but microscopic size the site of origin must be indistinguishable. We could not expect to be able to recognise the actual "malignant degeneration" of the endothelial cells of pre-existing vessels except in very rare instances and by extreme good fortune. The close association of tumour cells with blood vessels which has been brought forward as indicating their endothelial origin might just as well be explained by permeation within the lumen of the vessel or in the perivacular lymphatics, or by the survival of tumour cells which are adjacent to blood vessels and are therefore less susceptible to the degenerative changes of malnutrition. We need not consider the obvious fallacy of hæmorrhage into a tumour of loose texture, for this should not demand serious discussion.

With regard to the formation of lumina in general, it is necessary to realise that this process is quite common in the simple carcinomata. Before such spaces can be considered as being in any way indicative of a growth of endothelial cells, it must be certain that they are not simply the result of degenerative changes; therefore, the cells lining the lumina must be as healthy and well formed as those at the periphery.

Lack of differentiation of the tumour cells, and failure on their part to form tubules or acini, must not be considered as negativing the possibility of the carcinomatous nature of a neoplasm. In the carcinoma simplex there is no hint of the glandular origin of the tumour, nevertheless, as we have seen, all stages can be traced between this form of cancer and the adenocarcinoma. Similarly, the cells of a typical squamous carcinoma may in certain areas lose all differentiation; there may be no prickle cells and no keratinisation. Again, the cells of a carcinoma simplex, when growing in solid alveoli, may exhibit appearances strongly suggestive of "whorl formation"; and the assumption by the cells of a squamous carcinoma of a spindle form is well recognised. It seems, then, that unless the whorl formation is very distinct, it is unjustifiable to place too great a reliance upon what may be, after all, quite a secondary phenomenon.

A study of inflammatory lesions teaches us that the endothelial cell is peculiarly liable to form giant cells, and because of this some pathologists are inclined to regard the presence of giant cells in a tumour as strong evidence of its endotheliomatous origin, especially in combination with a marked variation in the size of the parenchyma cells. But it is in a rapidly growing carcinoma that we might be prepared for just such features as irregularity in the size of the cells, abnormal forms of cell division with the production of giant cells, and absence of any glandular structure; so that this line of argument is not very convincing.

Enough has been said to make it clear that the atypical endothelioma can scarcely be regarded as having an established position, and it is, perhaps, permissible to add that a serious obstacle in the way of their universal recognition exists in the natural reaction which has followed the indiscriminate use of the term in the last few years. There has been far too great a tendency to name any unrecognised or anomalous tumour an endothelioma, and though such a course may have its immediate advantages, it has helped not a little to obscure an already sufficiently difficult subject.

It will be convenient for our purpose to divide the Endotheliomata into three groups:

I. Vascular endotheliomata.
II. Lymphatic endotheliomata.
III. Endotheliomata growing in connection with serous membranes.

I. **Vascular Endotheliomata.**—Tumour growth of the lining cells of blood vessels may be accompanied by a proportional proliferation of simple connective tissue, or it may not. In the former case the resulting tumour will be a histioma, in the latter a cytoma. It is doubtful whether the majority of the vascular histiomata, or angeiomata, should be included among the blastomata at all ; they are rather in the nature of dilatations and elongations of pre-existing vessels than true new formations. It is usual, however, to recognise two main types, the capillary angeioma, and the cavernous angeioma.

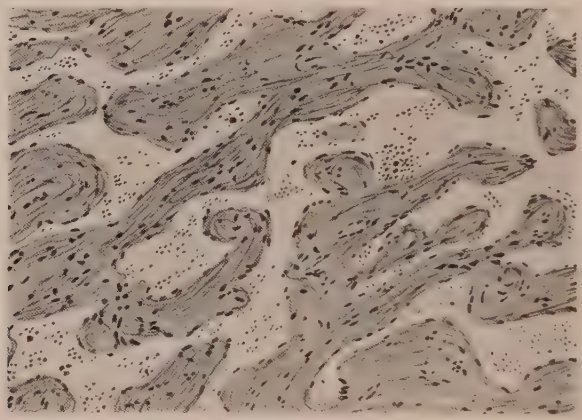

Fig. 87.—Microscopic section of a cavernous angeioma of the liver showing irregular thick-walled blood-containing spaces with an imperfect endothelial lining.
Obj. 8 mm. apochrom. Comp. oc.4. Tube length, 160 mm.

The ***capillary angeioma*** (telangiectasis) is a tumour composed of groups of capillary vessels containing fluid blood. The capillaries are of unequal size, and their walls are extremely delicate, consisting of little more than endothelium supported by a scanty stroma of connective tissue. Many of these growths are congenital, and this is notably so in the skin, where they form the familiar vascular nævus, or birth-mark. Apart from the skin, they are also found in the subcutaneous tissue and in muscle. Of the greatest importance is the capillary angeioma of the pelvis of the kidney, for although it is quite small it may give rise to fatal hæmorrhage. Similar talengiectases of mucous membranes may occur in other situations.

The ***cavernous angeioma*** is found chiefly in the liver, where

it is the commonest type of new growth. The tumours may attain to a considerable size and are frequently multiple. Like the capillary angeioma, this form consists of a collection of blood-containing spaces, but it differs in that the capillary walls are thick and are composed of fairly dense fibrous tissue (Fig. 87).

In the case of the vascular nævus it is patent that we are dealing with a congenital malformation rather than a blastoma, and though the other angeiomata may not reveal their blastomatoid nature so obviously, we should exercise considerable caution before placing any one of them among the true neoplasms.

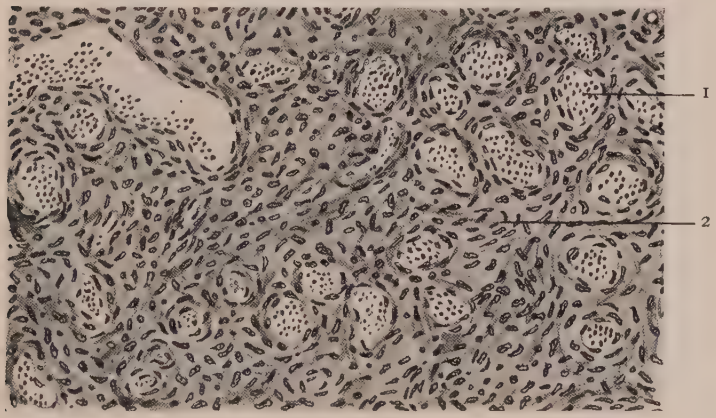

Fig. 88.—Microscopic section of an hæmangeioma simplex showing capillary blood vessels (1) surrounded by proliferated endothelial cells (2).
Obj. 8 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

Hæmangeioma Simplex.—These tumours occur as a rule in the subcutaneous tissues, where they form small lobulated growths; an early stage in their formation may often be seen in the walls of bursæ. They are composed essentially of large endothelial cells, which are arranged in several layers around blood-containing tubules (Fig. 88); sometimes very few tubules are present, and the cells form solid columns. There is only the smallest amount of connective tissue uniting the separate lobules.

The hæmangeioma simplex is an innocent tumour, though it is said to give rise occasionally to metastases. It is never definitely localised or encapsuled, however, but has remarkable powers of infiltration; its margin is ill-defined, and it extends widely in the subcutaneous tissues or among adjacent muscle bundles.

The hæmangeioma simplex has many of the characteristics of a true neoplasm rather than a blastomatoid process, but the fact that its tubules contain circulating blood raises a very interesting point, for it implies a physiological connection with the neighbouring healthy vessels. It is quite possible for such a connection to exist between an innocent blastoma and the parent tissue from which it took origin, but there are certain tumours which, while still retaining their association with healthy

Fig. 91.—Section of a sinus in the tumour illustrated in Fig. 89 showing the "solid" type of endothelial growth seen also in Fig. 90.

vessels, present all the histological characters of malignancy. It is difficult to understand how this can occur. The only reasonable explanation is that the tumour mass is constantly being added to by the progressive malignant transformation of the cells of healthy capillaries in the neighbourhood; but this conception is opposed to all we know of the origin of neoplasms, and we are forced to the conclusion that these tumours are in reality blastomatoid processes.

A tumour of this nature is illustrated in Figs. 89-92. It was situated among the muscles of the back in an infant, and though its vascular nature is quite obvious in places, elsewhere its

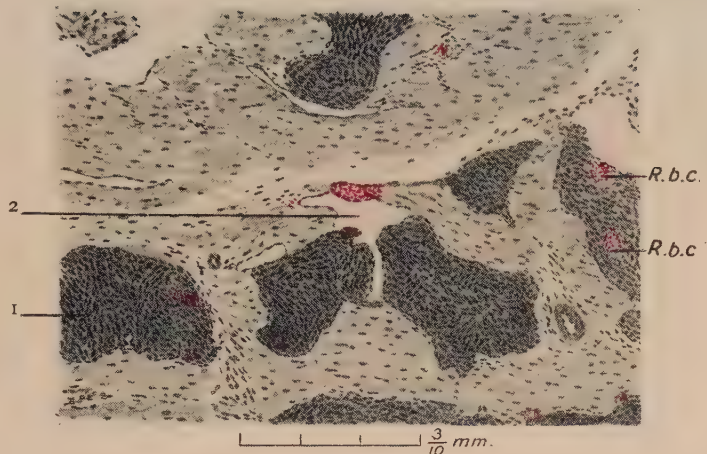

FIG. 89.—Section of a malignant hæmendothelioma of the muscles of the back. The tumour consists of solid areas of growth having the structure of a spindle-celled sarcoma (1). These are associated with large blood-containing sinuses (2). Compare with Figs. 90-92.

FIG. 90.—A large sinus in the tumour illustrated in Fig. 89. It is filled with papillary ingrowths of the lining endothelium. Some of these papillomata are solid (*A*), but others consist simply of coiled capillaries (*B*).

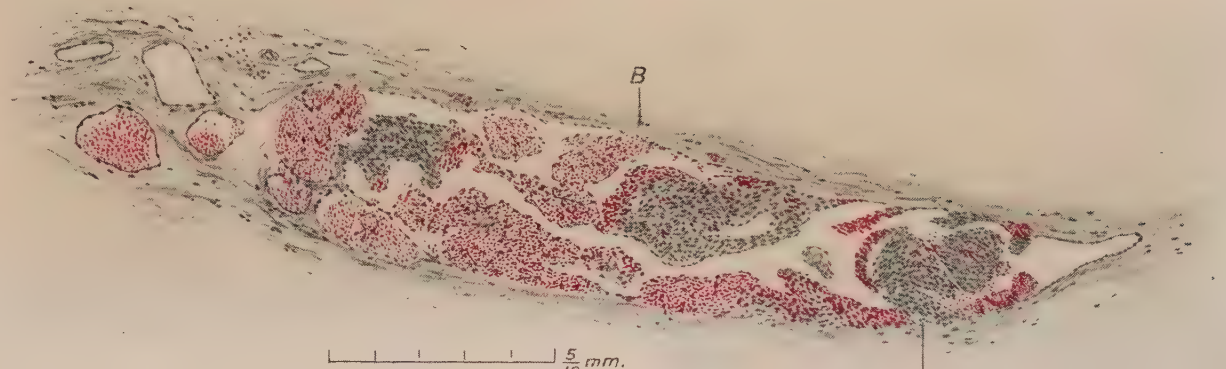

PLATE IV

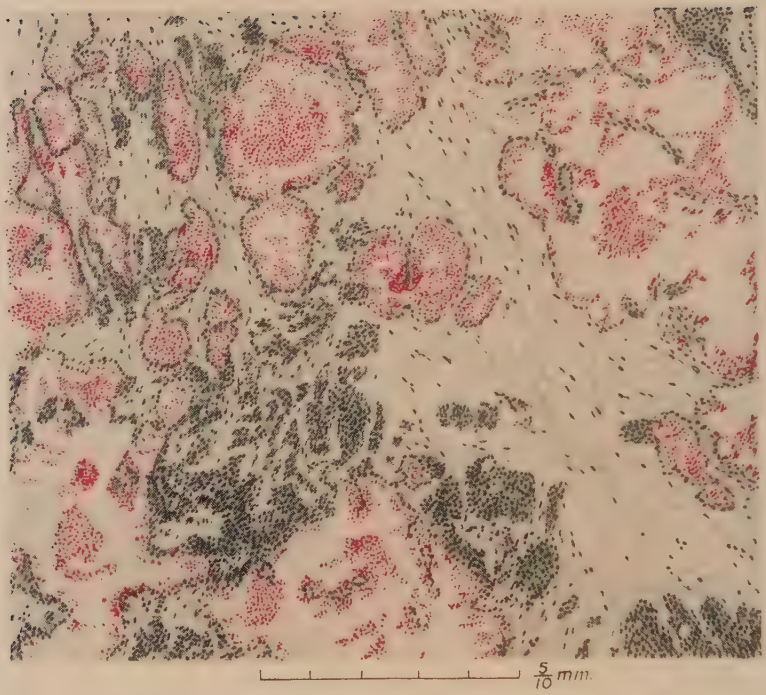

Fig. 93.—Section of a malignant hæmendothelioma showing large spaces containing fluid blood, and solid areas of growth. Compare with Figs. 94-97.

To face p. 173.

structure closely resembles that of a spindle-celled sarcoma. The solid areas of growth are all associated with dilated capillaries (Fig. 89), and are formed by the proliferation of their lining cells (Figs. 90 and 91), and the capillaries themselves communicate directly with perfectly normal veins (Fig. 92).

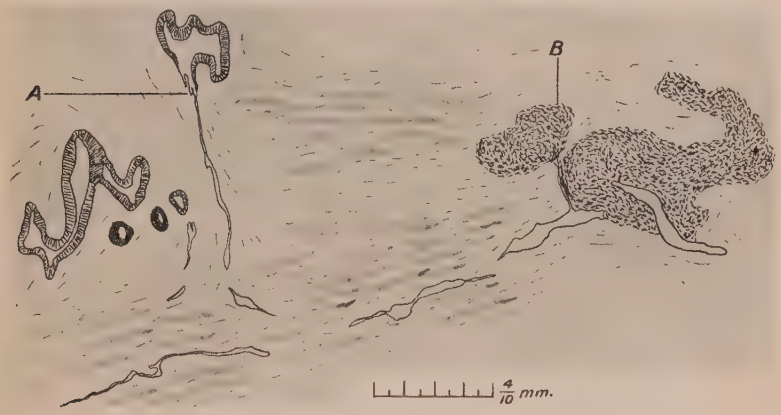

Fig. 92.—Section from the periphery of the tumour illustrated in Fig. 89 showing a complex system of capillaries which communicate with a normal vein at *A*, and with a nodule of growth at *B*.

Malignant Hæmendotheliomata.—These tumours are cytomata, and though they present evidence of their vascular origin, they are atypical in their structure and do not reproduce tissues. But inasmuch as they exhibit a wide range of differentiation, a study of them enables us to distinguish the characteristic features by which we may recognise the neoplastic endothelial cell. The tumour illustrated in Figs. 93-97 is particularly instructive. The general structure is shown in Fig. 93. The most striking feature is the occurrence of large irregular spaces which contain fluid blood. Sometimes they possess a thick lining of spheroidal cells, but more often the lining is reduced to a single or double layer, and it may be absent altogether. Associated with these vascular elements are areas of more solid growth. These consist of cells which are grouped loosely or compactly in large or small masses without any intercellular substance. The actual cells vary enormously in size and shape so that no typical forms exist, but they present, nevertheless, characteristics which place their origin beyond

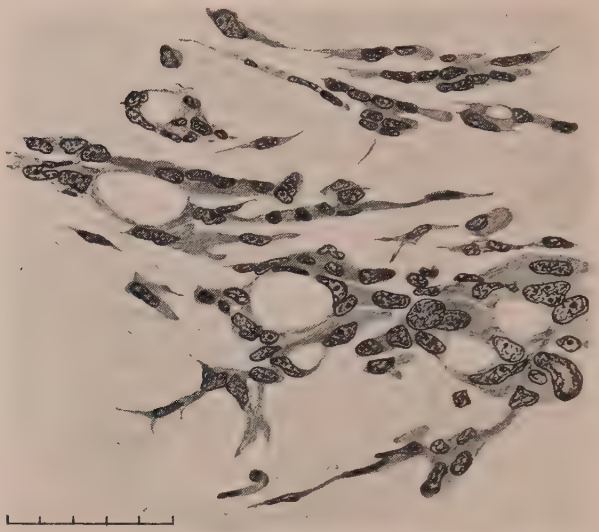

FIG. 94.—Section from the periphery of the tumour (Fig. 93) showing the vasoformative type of cell. The tumour cells grow as branching, vacuolated syncytia.

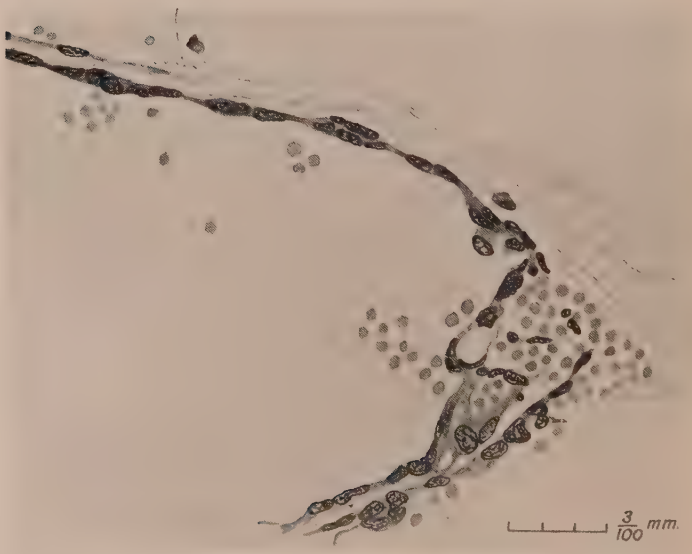

FIG. 95.—The cells of the tumour are forming the endothelial lining of a blood space.

doubt. At the growing margin branching syncytial forms occur which bear a striking resemblance to vasoformative cells (Fig. 94), and when growing in looser tissues these syncytia may be drawn out as a flattened lining to a blood-containing space, that is to say, they form an endothelium (Fig. 95). And however variable the tumour cells may be in most respects, one very constant feature is the occurrence in the cytoplasm of vacuoles which do not contain fat but are apparently the result of a simple

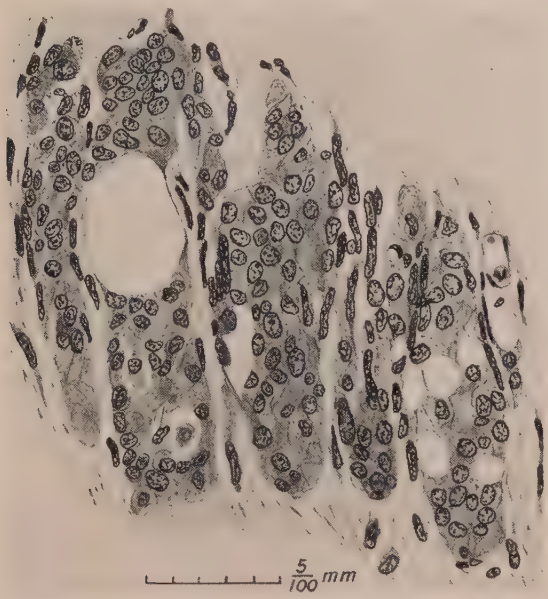

Fig. 96.—Section of a solid area of the growth illustrated in Fig. 93. Vacuoles appear in the cells, and these by their coalescence form large spaces.

hydropic degeneration. Figs. 96 and 97 show how the large bloodspaces of the tumour are formed from solid cell masses by the development and coalescence of these vacuoles. A similar process occurs normally in the formation of new vessels, whether they are derived from budding of the endothelium of pre-existing capillaries, or whether they arise from the growth and fusion of the vasoformative cells of the mesoblast. In the tumour, the large spaces result from a degenerative process in the essential cells of the neoplasm, a process which has its counterpart in the physiology of the normal angeioblast, though it is quite

uncontrolled in the malignant cell. Tumours of this type have no physiological connection with the vascular system of the host; there is no true circulation of blood within them, but the spaces merely contain blood because it is effused into the tissues from capillaries of the stroma which have been infiltrated and ruptured by the growth of the tumour cells.

It is from the study of such tumours as this that one may hope to establish the standards by which the neoplastic endothelial cell can be recognised. The negative properties of a cell cannot demonstrate its origin, and it is only when the cells of a neoplasm present positive evidence of their endothelial nature that we are justified in calling the tumour an endothelioma. It is not claimed, of course, that the endothelial cell has no other functions than the formation of capillaries or endothelia; it plays an important part in many inflammatory reactions, and frequently breaks loose to become a free wandering cell. But in these circumstances it loses its distinctive characters and can only be recognised with difficulty. Similarly it is quite possible that many of the anomalous tumours met with from time to time may consist of atypical neoplastic endothelial cells. But since this cannot, at present, be proved, there is no justification for labelling such tumours as endotheliomata.[1]

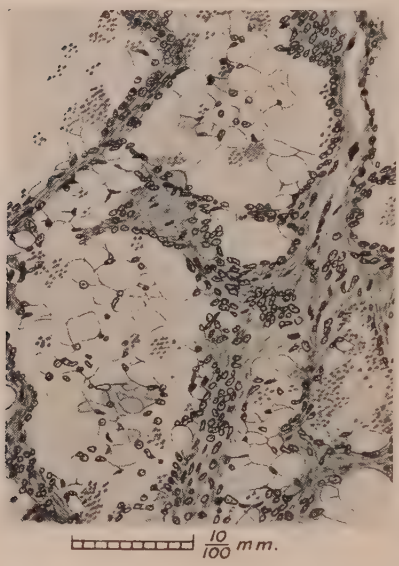

FIG. 97.—A more advanced degree of the cell vacuolation seen in Figs. 94 and 96. By the fusion of neighbouring vacuoles large spaces have formed into which blood has oozed.

A rare form of endothelioma is the "hæmangeiosarcoma" of bones. In this tumour the capillary formation is maintained, but the lining endothelium becomes cubical or even columnar in shape, so that the likeness to an epithelial growth is very

[1] See also Kettle, *Proc. Royal Soc. Med.*, 1918, vol. xi. (Path.), p. 19. and Kettle and Ross, *Lancet*, 1921, i. p. 1012.

close. It is likely that many of the so-called endotheliomata of bones are in reality metastatic carcinomata.

II. **Lymphatic Endotheliomata.**—It is possible to distinguish similar progressive changes in the lymphatic vessels and their lining cells, but, in the absence of blood, their recognition may be a matter of difficulty.

The ***simple lymphangiectasis***, corresponding to the vascular nævus, consists of collections of dilated lymph vessels, and is usually situated in the skin of the face and neck. . It is congenital

Fig. 98.—Microscopic section of a cavernous lymphangeioma of the back. The tumour consists of a collection of thick-walled spaces lined by proliferated endothelial cells.

Obj. 16 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

in nature. Closely associated with this condition is the ***cystic lymphangiectasis.*** Here, combined with an active secretion into the lumina of the capillaries, there is obstruction to the outflow of the fluid, with a consequent dilatation of the tubules. The best-known example of this process is seen in the ***cystic hygroma*** of the neck. This is composed of a collection of large spaces containing clear lymph, and bounded by fibrous tissue lined by endothelium.

The ***cavernous lymphangeioma*** has a structure comparable with that of the cavernous angeioma (Fig. 98). It is the underlying process in such congenital conditions as diffuse enlargement of the lip and tongue, known as macrocheilia and macroglossia respectively.

True lymphatic blastomata occur in the subcutaneous tissues and muscles, but they are rare. In some of them the growth is mostly solid, but in others a multitude of large spaces are formed, lined by a swollen endothelium. Sometimes the tumour consists of innumerable minute tubules lined by endothelial cells which are only slightly larger than the normal (Fig. 99).

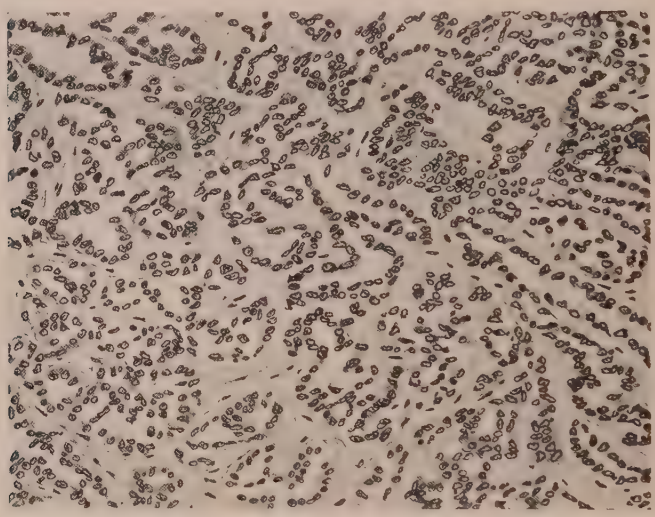

Fig. 99.—Microscopic section of a lymphendothelioma of muscle. Obj. 8 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

III. **Endotheliomata growing in Connection with Serous Membranes**.—The most important members of this group are the endotheliomata of the dura mater. Nearly all these tumours are situated on the inner surface of the dura lining the skull, but they sometimes grow in the vertebral canal, or on the sheaths of the cranial nerves.

In spite of their situation in respect to a serous membrane, it is possible that many of the tumours grow from the endothelium of capillary vessels, and not from the lining cells of the membrane. They form nodular growths or thick plaques, and frequently contain calcareous nodules, the so-called psammoma bodies.

Microscopically (Fig. 100) they consist of cells of the endothelial type, sometimes short and plump, sometimes thin and

drawn out, which have a characteristically whorled arrangement. Some of the whorls are restricted in their extent, the cells being closely grouped around capillary vessels; elsewhere they appear to form part of a wider system. Often there is no central capillary, but the cells in the middle of the whorl are tightly packed together in solid columns. Occasionally multinucleated giant cells are formed. When present, the psammoma bodies

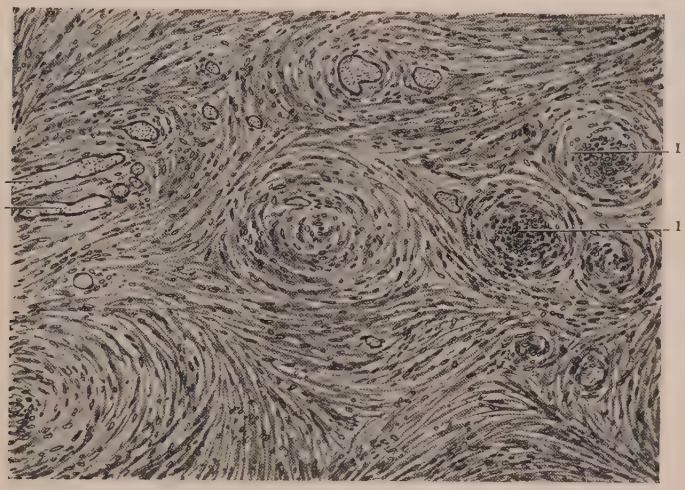

FIG. 100.—Microscopic section of an endothelioma of the dura mater. The tumour is composed of long drawn-out cells having a "whorled" arrangement which occasionally results in the formation of solid columns of cells (1); there are numerous capillary blood vessels (2).

Obj. 8 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

are seen to consist of small spherical nodes having a laminated structure. They represent small groups of the tumour cells, which have become infiltrated with calcium salts.

The dural endotheliomata may be innocent or malignant. In the latter case it is usual for the cells to become definitely of the sarcomatous type, the tumours resembling an ordinary spindle-celled sarcoma. But this is not invariably the case, and the tumours may exhibit an infiltrative growth, invading even the bones of the skull, while at the same time they retain the typical histological appearance.

The ***psammoma*** is another endotheliomatous tumour growing in connection with the cerebral membranes. It is a small nodular growth, and is hard and calcareous throughout. *Microscopically*

(Fig. 101) it consists of concentrically laminated calcareous bodies, bound together by a somewhat delicate connective tissue network. This connective tissue is often highly vascular, and the endothelium of the capillaries shows a tendency to proliferation.

The majority of psammomata appear to be simply angeiomata in which calcification has occurred as a secondary phenomenon, either in capillary thrombi, or in groups of proliferated endothelial cells, or even in the walls of the smaller vessels.

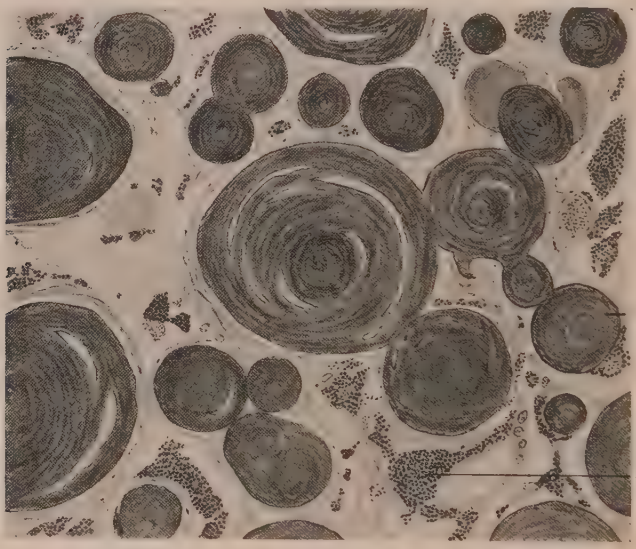

Fig. 101.—Microscopic section of a psammoma of the dura mater, showing concentrically laminated "psammoma bodies" (1) lying in a loose connective tissue stroma in which occurs groups of proliferated endothelial cells (2).
Obj. 16 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

Following the accepted teaching, these tumours arising from the dura mater have been classed as endotheliomata. It must be admitted, however, that many of them are difficult to distinguish from fibroblastomata. Mallory [1] denies their endothelial origin. According to him there is no dural endothelium, but the inner surface of the dura is bare except for fibroblasts, and he holds that all these growths are derived from fibrous tissue.

Tumours of the pleura and the peritoneum are not common. Both innocent and malignant forms are described, occurring as

[1] *Journal Med. Research*, 1920, v. xli., No. 3, p. 349.

nodular and flattened growths, often spreading widely over the surface of the membrane. They are composed of endothelial cells, often exhibiting an irregular acinous arrangement, enclosed in a fibrous stroma. They are like epithelial neoplasms in their histology, but the more malignant forms have a very atypical structure and more closely approach the alveolar sarcomata (Fig. 102).

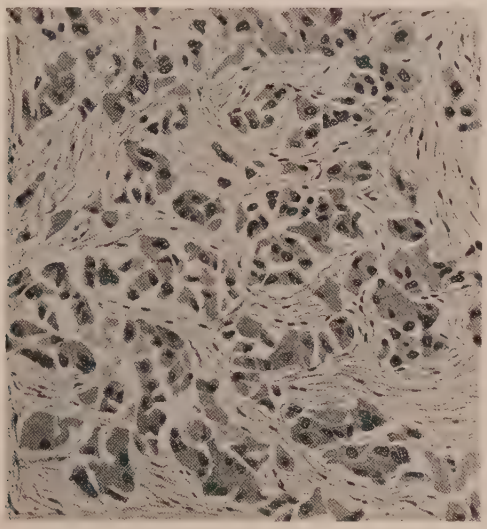

Fig. 102.—Microscopic section of an endothelioma of the pleura. The tumour cells vary considerably in size and shape, and are loosely grouped together in irregular acini.

Obj. 8 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

In this group may be included the ***Myeloid*** or ***Giant-celled Tumours*** of tendon sheaths, though there is still some doubt not only as to whether they are true blastomas but also as to their endotheliomatous nature. They are firm, lobulated tumours which grow slowly from tendon sheaths or deep fascia. They are quite innocent, though local recurrence may of course occur after imperfect removal. *Microscopically* they show a basis of fibrous tissue in which occur spheroidal or polygonal cells which are often loosely packed together in alveoli. Associated with these cells are a varying number of giant cells of the "myeloid" type. Many of the tumours contain a considerable quantity of hæmosiderin, and in some there occur numerous foamy, xanthoma cells which contain anisotropic fat (Fig. 120).

THE HYPERNEPHROMATA

The hypernephromata form but a small class, and have a restricted distribution, yet they present such characteristic features, and have been the subject of so much controversy, that a separate description of them would seem to be quite justified.

The term hypernephroma is applied to a particular group of tumours, in the belief that they are derived from suprarenal tissue. Theoretically, the tumours may arise in the adrenal gland itself or in certain other situations, but, as a matter of fact, the great majority of them occur in the kidney, and it is extremely rare to find them elsewhere.

This chapter, then, will consist largely of a discussion of the hypernephromata of the kidney; and, in passing, it may be pointed out that most of the renal tumours of any clinical importance are included in this category.

The renal hypernephromata usually occur between the thirtieth and fiftieth years; they may arise in any part of the cortical tissue of the kidney, about an equal number of cases starting in the upper and lower poles, and a rather higher proportion in the middle zone. The tumours are spherical in shape; they project to a considerable extent above the limits of the kidney, and their surfaces are often nodular. On section they are seen to be surrounded by a well-marked capsule of condensed renal tissue, but the growth has a tendency to burst through this capsule and form daughter nodules, which, in turn, themselves become encapsuled. In time, almost the whole of the kidney may be invaded, and at quite an early stage the growth may extend into the pelvis. In advanced cases extension may also take place into the renal vein, and columns of growth mingled with blood clot may reach into the inferior vena cava.

The naked-eye appearance of a hypernephroma is very characteristic, and renders it possible to make a diagnosis from a macroscopic examination in a high proportion of cases.

In typical examples there is a primary encapsuled tumour surrounded by daughter tumours, which diminish in size as the limits of the growth are approached. Unaltered areas of tumour tissue are of a yellowish colour, but the cut surface has usually a mottled, deeply hæmorrhagic appearance, for the growths are exceedingly vascular, and there is nearly always an extensive

extravasation of blood (Fig. 103). Central cystic degeneration of the larger nodules may occur, but more commonly there are

Fig. 103.—Hypernephroma of the kidney, showing degenerative changes and encapsulation of the primary growth and the daughter tumours. The remains of the kidney can be seen in the upper part of the specimen.

areas of mucoid degeneration mingled with zones of dense fibrosis, the appearance as a whole suggesting very strongly the presence of cartilage.

The *microscopic* structure is of great interest. The tumour cells are cuboidal in shape, but they are liable to become distorted as the result of mutual pressure ; sometimes they are distinctly columnar. They have a small, round, deeply staining nucleus, and are distinguished by the clear, vacuolated appearance of their cytoplasm, an appearance due partly to hydropic distension,

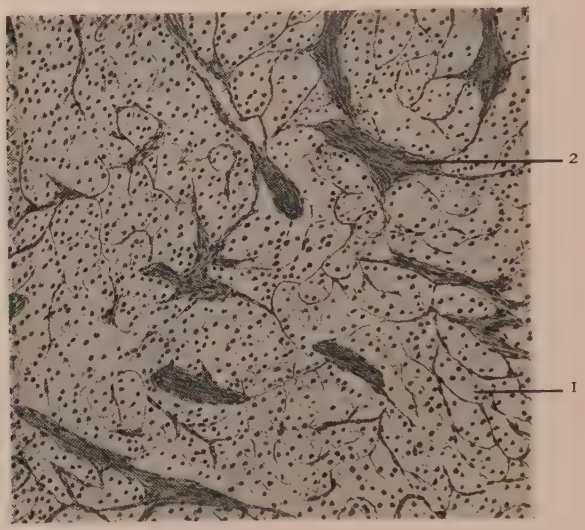

Fig. 104.—Microscopic section of a hypernephroma of the kidney. The tumour cells are clear and vacuolated, and have a trabecular arrangement (1). The tumour is traversed by coarse strands of fibrous tissue (2).
Obj. 16 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

partly to the solution, in the process of preparation, of the fat and glycogen present in the fresh state. Their arrangement is extremely variable.

Trabeculæ or solid alveoli are common (Fig. 104), and the latter may exhibit a lumen from the degeneration of the central cells. In some tumours there is a true acinous formation (Fig. 106), and in others the cells are often disposed in a papillomatous manner around a vascularised connective tissue core (Fig. 107). Occasionally cystic spaces, which may be partly filled up by an ingrowth of the lining cells, are formed, and every now and again the cells may be loaded with pigment granules, probably as the result of old hæmorrhages.

Except in the older parts of the tumour the stroma is always

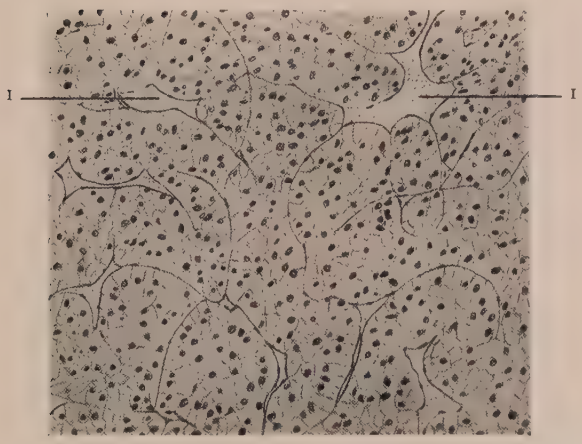

FIG. 105.—Microscopic section of a hypernephroma of the kidney, showing a solid, trabecular type of growth, and close relationship of the tumour cells to the large capillary vessels (1).

Obj. 8 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

FIG. 106.—Microscopic section of hypernephroma of the kidney showing a tubular type of growth. The drawing was made from another part of the same section illustrated in Fig. 104. (1) Tubule lined with cubical cells; (2) large capillary blood vessels.

Obj. 8 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

extremely scanty, and the groups of cells are separated by, and rest upon, delicate capillaries which consist of little more than tubes of endothelium (Fig. 105). The vascular supply is always abundant, and the capillaries are often dilated into large sinusoids.

Clinically, the renal hypernephromata give rise to very few symptoms, the most common being recurrent attacks of hæmaturia, often after some unusual exertion, and a varying amount of backache. For the most part the growth appears to be slow,

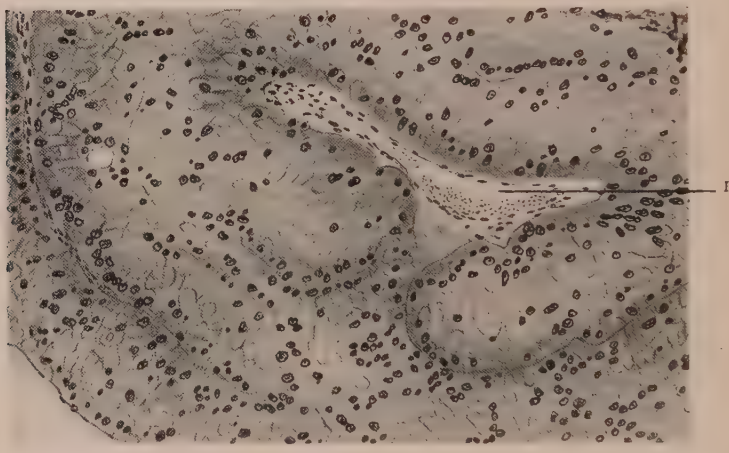

Fig. 107.—Microscopic section of a hypernephroma of the kidney showing the papillomatous arrangement of the columnar tumour cells around a blood vessel (1). Obj. 8 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

and the formation of secondary deposits is delayed, so that, although the perinephric tissues are usually invaded and adherent to the tumour, a complete removal offers a fair prospect of a cure. But every tumour should be regarded as having malignant potentialities.

When dissemination does take place, the secondary deposits are prone to appear in the lungs and in bones. The lymphatic glands may also be affected, and I have been informed of cases where a hitherto unsuspected hypernephroma was diagnosed by an examination of, and the demonstration of metastases in, an enlarged gland. Quite often the first clinical symptom is the appearance of a bony metastasis which is usually diagnosed as a primary sarcoma. Malignancy may be associated with a

more sarcomatous type of cell, but, in my experience, if the local recurrences and metastases differ at all histologically from the primary tumour it is in the direction of a more frankly carcinomatous structure.

There has always been a considerable divergence of opinion as to the nature of the renal hypernephromata, and the matter cannot be considered as settled even now. Formerly, they were

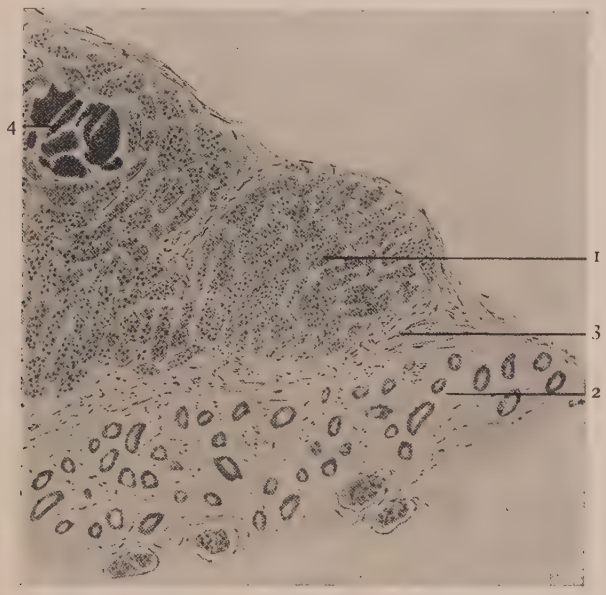

FIG. 108.—Microscopic section of an adrenal "rest" on the surface of the kidney. The "rest" (1) is separated from the kidney tissue (2) by the kidney capsule (3). At (4) is a small adenomatous nodule.

Zein Obj. aa. Comp. oc. 4. Tube length, 160 mm.

described under a variety of names, lipoma, sarcoma, angeiosarcoma, carcinoma, and endothelioma; but in 1883 Grawitz demonstrated the presence of "rests," or misplaced fragments of suprarenal tissue on the surface of the kidney, and suggested that the origin of these tumours should be sought for in them.

It was an attractive theory, and immediately became popular. Nevertheless it did not receive universal acceptance, but was, from time to time, subjected to damaging criticism.

Put briefly, the argument in favour of the origin of the hypernephromata from misplaced fragments of the suprarenal gland

is as follows. Such " accessory adrenals " are known to occur with some frequency : they are particularly common on the surface of the kidney (Fig. 108), and may also be found in the liver and on its under surface, in the retroperitoneal tissue along the course of the spermatic and ovarian vessels, in the broad ligament, and in the spermatic cord. That such " rests " should be the subjects of atypical cellular proliferations is quite a reasonable supposition, and one well in accord with Cohnheim's theories. The tumours themselves, with their bright yellow colour, closely resemble adrenal tissue ; and the histological structure, the trabecular arrangement of the clear vacuolated cells, is very similar to that of the zona fasciculata of the suprarenal gland. That the cells of hypernephromata contain fat and glycogen was also considered to be a strong point in favour of their origin from adrenal tissue ; but both these substances may be present in other neoplasms, and this argument, therefore, carries little weight.

So far, a strong case would seem to have been established, but a more critical consideration raises very cogent doubts as to the validity of the conclusions which have been arrived at.

In the first place, Why is it so rare to find hypernephromata anywhere except in connection with the kidney ? Instances have certainly been recorded of such extrarenal tumours in the liver and the broad ligament ; but whereas hypernephromata are quite common in the kidney, very few investigators have had the good fortune to encounter them elsewhere. It may be objected that the " rests " occur in the kidney with much greater frequency than in other situations, but there is very little positive evidence in support of this contention, for it must be remembered that the surface of the kidney is examined practically always at an autopsy, while the broad ligaments and the spermatic cords are subjected to a much less searching scrutiny. With regard to the kidney itself, a systematic examination of all the cortical tumours, even to those of the minutest size, encountered throughout a fairly extensive post-mortem experience, has convinced me that only a small proportion of them consist of misplaced adrenal tissue ; by far the greater number are primary kidney adenomata. From the anatomical relations of the kidney and the suprarenal gland one would expect to find the majority of the hypernephromata in the upper pole of the kidney were they derived from adrenal rests ; but, as we have seen,

this is not the case. Similarly, the small whitish or yellow tumours found on the surface of the kidney, and usually termed "adrenal rests," may occur in any part of the organ.

Again, a suprarenal rest on the surface of the liver can scarcely escape notice in the course of an ordinarily careful examination, but I have never yet encountered one. So that, while fully acknowledging the occurrence of such rests, especially in relation to the kidney, it seems probable that their frequency has been somewhat exaggerated.

A histological study of hypernephromata reveals several points of difference between the structure of these tumours and that of the adrenal glands.[1] In the hyperplasias and neoplasms of the latter a solid structure is the rule; one never sees a papillomatous formation, and only rarely is there any suggestion of the production of acini or tubules, whereas both of these are common enough in the hypernephromata. Further, there is a very striking likeness between many of the malignant renal tumours and the small adenomata so often found on the surfaces of granular kidneys. From a consideration of the histological features, therefore, one is forced to the conclusion that the so-called hypernephromata are really renal in origin.

Opinions are again divided on the question whether the tumours arise from mature kidney cells, or from rests of embryonic renal tissue. Stoerk [2] holds that they are derived from adult renal tubules in which the "tissue tension" has become disorganised as the result of a local or generalised chronic atrophic nephritis. Wilson [3] has approached the problem from the embryological point of view. While he believes that the hypernephromata arise in embryonic rests, he regards these rests as representing undeveloped areas of the kidney anlage, and not misplaced fragments of the suprarenal gland.

Nicholson [4] in an exhaustive and convincing paper strongly supports Stoerk's views. He concludes that "the hyperneophromata of the kidneys arise in the renal epithelium. No instance has been described whose origin in suprarenal tissue, assumed by Grawitz, is assured."

Tumours of the adrenal cortex itself are rare. Small nodular hyperplasias, or adenomata, are by no means uncommon, but

[1] Glynn, *Q. J. Med.* 5, p. 157, 1911-12.

[2] Ziegler's *Beiträge*, 1908. [3] *Journal of Medical Research*, 1911.

[4] Nicholson, *Guy Hospital Reports*, April 1923, p. 164.

malignant growths, or innocent tumours of any size, are seldom found—a fact of some significance in view of the preceding argument.

Adrenal hypernephromata are very much more malignant than the corresponding tumours of the kidney; they may be bilateral. They grow rapidly, invade lymphatic glands at an early stage, and are usually fatal in spite of operative measures.

A very interesting feature is the association of these tumours with the development of abnormal sex characters. Female children and women before the menopause tend to develop certain male sex characters, while boys show sexual precocity. Adult males are unaffected. The renal hypernephromata have never any effect on the sexual characters of the patient. It is true that renal hypernephromata are very rare in children, but they are not uncommon in adult females, and the fact that they are never associated in these patients with abnormal sexual characters is a strong argument against Grawitz's hypothesis.

With reference to the still rarer tumours, those occurring in the liver and elsewhere, there is little that need be said. But it is necessary to insist that a diagnosis is only to be made after careful consideration, and can seldom be free from all doubt. Accidental modifications of pressure and nutrition may profoundly modify the shape and structure of the cells of a malignant growth, and may give rise to highly anomalous appearances. In my own collection I have a section of a recurrent papilloma of the bladder which can scarcely be distinguished from another one, taken from a perfectly typical renal "hypernephroma" in which papillomatous areas alternated with others of a solid type of growth. Again, the cells of a primary carcinoma of the liver may bear quite a striking likeness to those of a hypernephroma; and this is also true of some of the carcinomata of the testicle. Anaplasia, or loss of its distinctive characters, is natural to the cancer cell, and we must be prepared for a certain similarity between the cells of different growths. So, however tempting it may seem to diagnose an obscure tumour as an hypernephroma, it is a difficult course to justify, and one only to be entered upon with much caution.

THE MELANOMATA

The melanomata differ from all other tumours in that their cells contain a variable amount of an iron-free pigment called melanin. Most of them grow from two situations, the skin and the choroid coat of the eye, but they are occasionally found elsewhere, in connection with the membranes of the brain, for example, or in the gall-bladder or the lower part of the rectum. They are of great interest, not only from the diversity of their histological structure, but also from the point of view of their exact nature and origin.

The cutaneous melanomata have been more extensively studied than the other forms, and illustrate very well the points at issue. The simplest example of a melanoma, the pigmented mole, is one of the commonest abnormalities of the skin. It is a congenital formation, and occurs as a small warty tumour of a brown or blackish colour; some forms have a constricted base amounting almost to a stalk, but as a rule they are only slightly raised above the surface, and they may be quite flat. *Microscopically*, the tumour has a very definite structure, consisting of small groups of rounded, pigmented cells lying in a fairly dense fibrous tissue stroma; sometimes the cells may be seen to be congregated in the perivascular lymphatic spaces. The covering epithelium may show a papillomatous overgrowth, but it is more usually somewhat thinned and compressed, and the papillary processes are often much increased in size. Groups of the specific cells pass up in the papillary processes of the cutis, and may come into very intimate contact with the columns of epithelial cells (Fig. 109). The amount of pigment is by no means constant; the majority of the cells may be loaded with golden brown granules, or only a few cells here and there may contain them.

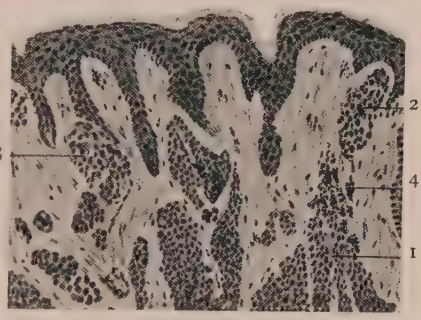

FIG. 109.—Microscopic section of a pigmented mole. The tumour consists of groups of spheroidal cells (1), often heavily pigmented (2); sometimes the cells come into close contact with the surface epithelium (3); masses of pigment lie free in the stroma (4). Obj. 8 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

It is generally agreed that the pigmented moles are derived from the chromatophores—the large pigment-bearing cells whose cytoplasm is prolonged into two or more processes—that are normally present in the cutis and the choroid coat of the eye, but there is still acute controversy as to the origin of the chromatophores. Some histologists, led by Unna, believe that they are epithelial in nature, being derived from the pigmented cells of the rete Malpighii ; others dissent strongly from this view, and regard them as being connective-tissue cells, and therefore of mesodermal origin. The source of the melanin is also uncertain, and we do not know whether it is derived from the hæmoglobin of the blood, or whether it is a degenerative product of the activity of the nucleus of the cell. If we are to look upon the epithelial cell as the sole source of melanin,[1] we are forced to accept Unna's view, for the neoplastic chromatophores do actually produce melanin ; they are true melanoblasts and are not merely carriers of pigment. The microscopic structure of many cutaneous melanomata suggests the direct origin of the chromatophores from the cells of the epidermis ; and the histological variations seen in some malignant melanomata are more compatible with an epithelial than a connective-tissue cell growth. But there is no general agreement in the matter, and the majority of authorities prefer to regard it as still *sub judice*.

Whatever may be the origin of the chromatophores, it is quite certain that from them are derived those highly malignant tumours known as melanotic sarcomata, nævocarcinomata or melanocarcinomata.

For no apparent reason, or perhaps as the result of some chronic irritation, a pigmented mole may assume an active growth, projecting above the surface of the skin, and frequently becoming ulcerated. With the increased rapidity of growth the histological appearances are markedly changed; the tumours become much more cellular, and the cells themselves present evidence of a heightened activity.

Sometimes these tumours may develop apart from pre-existing moles, often after some form of trauma. I have known three such tumours occurring on the feet, and ascribed by the patients in each case to previous injury with a rusty nail.

In an early stage it may not be easy to determine whether the growth is malignant or not, but in well-established cases the

[1] G. W. Nicholson, *Guy's Hospital Reports*, July, 1922.

diagnosis is quite clear. It may still be difficult, however, to decide as to the nature of the tumour, for two distinct histological types exist. In the one the structure, apart from the presence of melanin, is that of a spindle-celled sarcoma (Fig. 110); in the other the cells are polygonal or spheroidal in shape and have a solid alveolar arrangement, much more suggestive of a carcinoma (Fig. 111). Sometimes, even, a definitely adenomatous or acinous formation obtains (Fig. 112).

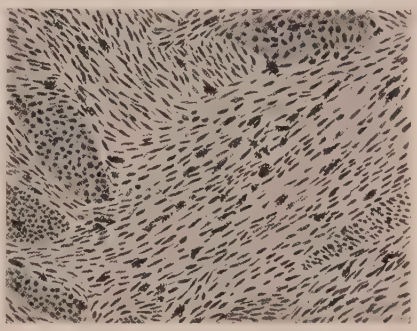

FIG. 110.—Microscopic section of a melanoma of the thumb, showing the sarcomatous type of growth. The tumour cells are spindle-shaped, and are grouped together in interlacing bundles. There is a moderate amount of pigment.
Obj. 8 mm. apochrom. Comp. oc. 4.
Tube length, 160 mm.

So marked are the histological differences that some authorities recognise two separate forms of pigmented neoplasms, the melanotic sarcoma and the melano- or nævo-carcinoma; the former arising

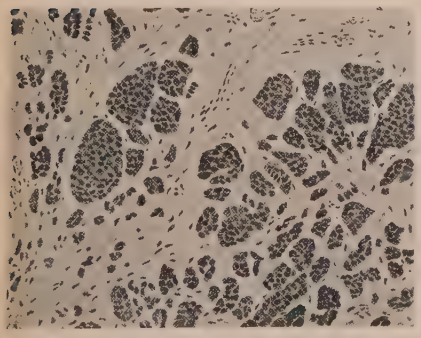

FIG. 111.—Microscopic section of a melanoma of the foot, showing the alveolar type of growth. The tumour cells are spheroidal in shape, and are grouped together in solid alveoli surrounded by an abundant stroma. There is no pigmentation.
Obj. 8 mm. apochrom. Comp. oc. 4.
Tube length, 160 mm.

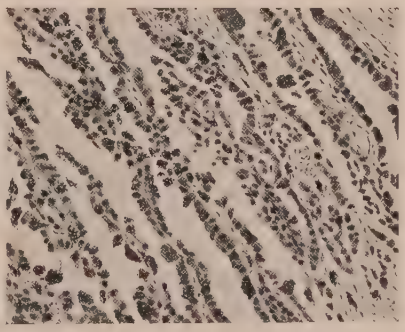

FIG. 112.—Microscopic section of a melanoma of the foot, taken from another part of the same tumour illustrated in Fig. 111. The tumour cells are irregularly cuboid in shape, and line elongated tubules. There is much formation of pigment.
Obj. 8 mm. apochrom. Comp. oc. 4.
Tube length, 160 mm.

from connective-tissue chromatophores, and the latter from the rete Malpighii of the epidermis.

The differences are, however, more apparent than real; tumours frequently exhibit all stages between the two types, and there seems no doubt that all melanomata are forms of one and the same class of new growths.

Both types may be met with in the skin, but the melanomata of the eye are nearly always frankly sarcomatous.

A prominent feature in the melanomata is the rapidity with which they disseminate, and the number and size of the metastases. A trivial, almost unnoticed, primary tumour may give rise to innumerable secondary growths affecting practically all the organs of the body. Dissemination by way of the lymphatic channels frequently takes place, especially in the cutaneous tumours; and the liver is particularly prone to be the seat of metastases, though these may be slow in declaring their presence.

The amount of pigment is variable, not only in the primary growth but also in the secondary deposits; some tumours may be quite pale, others of a deep black colour. As a rule, the sarcomatous type is heavily pigmented, while the alveolar growths contain only a few scattered granules. At times the tumour cells may degenerate completely, with the result that cysts filled with a black fluid are formed. So much pigment may be liberated in this way that it may appear in the blood and the urine.

THE TERATOMATA

So far we have been dealing with the autochthonous blastomas, tumours derived from unipotential cells native to the host or individual bearing them.

We have now to consider a group of neoplasms of a more complex structure and origin.

A teratoma or embryoma is a tumour containing organs or distinct fœtal structures, representatives of all three primitive layers of the blastoderm. A more precise definition (Adami) is: an autonomous growth, the product of the continued development within one individual of another individual of the same species.

It will be seen that certain tumours have been included in this section although they do not conform to the above definition. This has been done as a matter of convenience, since they are

either heterochthonous or are derived from pluripotential cells, in either case differing distinctly from the autochthonous blastomas. The subject is one of great interest, but anything approaching an exhaustive survey of it would be outside the scope of the present work. It is therefore proposed to treat of only the more important examples.

Using Adami's nomenclature, the following groups of teratomata and teratoid tumours may be distinguished.

I. Autochthonous teratomata—Tumours derived from totipotential cells of the individual.

II. Teratoblastomata—Autochthonous tumours derived from pluripotential cells of the individual.

III. Heterochthonous blastomata—Tumours derived from unipotential cells of another individual.

I. Autochthonous Teratomata

The commonest and most important examples of this group are seen in the ovary and the testicle. Extragenital teratomata are rare and of little practical interest apart from the question of their etiology. They occur in the thorax, abdomen, and cranium, and also grow from the lower part of the vertebral column, where they form the well-known ***sacrococcygeal tumour***. They may be innocent or malignant, and their structure is extremely complicated.

Ovarian Teratomata.—These tumours occur usually in early adult life and may be present in quite young children. They are often bilateral, and they may be multiple in the same organ.

Two forms are to be distinguished, the cystic and the solid, the former, the familiar " dermoid cyst," being by far the commoner.

The dermoid cyst may be uni- or multi-locular, and may attain to a considerable size. It is filled with a caseous, pultaceous material in which are to be found bundles or long strands of hair. The hair may be free in the cavity, but is more often attached to a nodular projection, the representative of the anterior extremity of the embryo, on the inner surface of the wall. Teeth are sometimes inserted into the wall around the base of this nodule.

The cyst wall is lined by squamous epithelium beneath which are many sweat and sebaceous glands (Fig. 113). Other tissues, cartilage, bone, muscle, and glandular and nervous elements

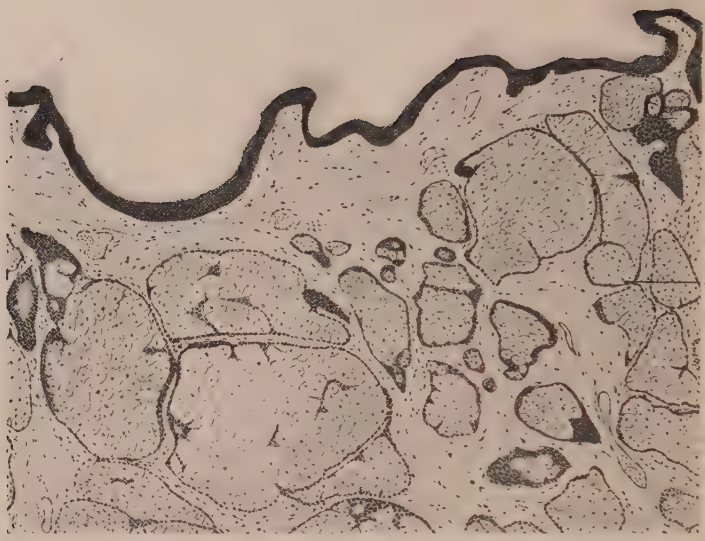

FIG. 113.—Microscopic section of the wall of a dermoid cyst of the ovary, showing the lining of squamous epithelium (1) beneath which are many sebaceous glands (2).
Obj. 16 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

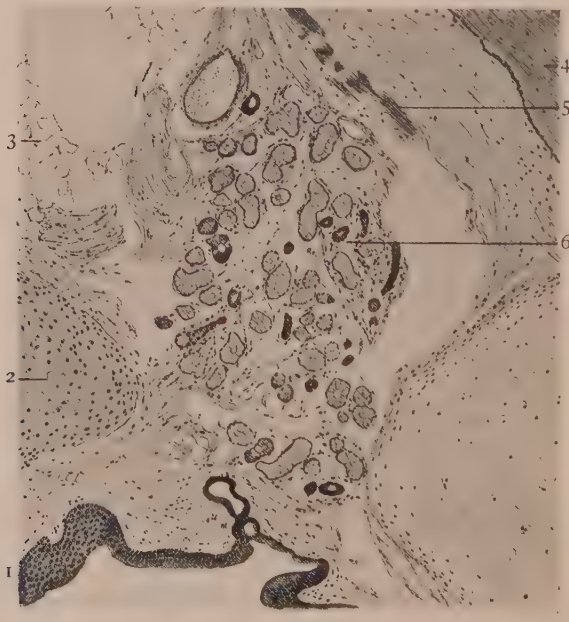

FIG. 114.—Microscopic section of a teratoma of the ovary showing stratified epithelium (1), cartilage (2), fat (3), osteoid tissue (4), bundles of smooth muscle fibres (5), and mucous and serous glands (6).
Obj. 16 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

are also frequently to be found (Fig. 114), and they may be so arranged as to resemble the structure of organs such as the trachea or the intestine. This is particularly the case in the nodular protuberance or head.

The solid ovarian teratoma is a rare tumour, and a malignant one. It exhibits the same mixture of tissues and cells as the cystic variety, though they are of a more anaplastic type. This tumour tends to disseminate, and the metastases may be of the mixed cell type or may consist of cells of one order.

Testicular Teratomata.—These, on the other hand, are nearly always solid tumours ; a dermoid cyst of the testicle is an extreme rarity. They occur in young adults, and form firm rounded tumours which, on section, present a variable picture. In the commonest form the growth consists of a dense, somewhat pale tissue in which are innumerable tiny cysts. Sometimes the cysts are larger, giving a spongy appearance to the growth, or there may be a disproportionate dilatation of one or more of them. Some tumours are more solid, containing few macroscopic spaces, but showing hæmorrhage, œdema, and other degenerative changes. As a rule, however, the general structure is indicated in the name, ***fibrocystic disease,*** by which this tumour was formerly known (Fig. 148, p. 255).

Microscopically, a very usual structure is that of a collection of tubules, lined by columnar epithelium, and surrounded or separated by bundles of smooth muscle fibres, the whole lying in a loose fibrous tissue stroma (Fig. 115). Islands of squamous epithelium, hairs, and masses of cartilage are often present as well ; indeed, by a careful examination, derivatives of all three of the primary layers of the blastoderm can generally be made out. In many tumours cell differentiation may be rudimentary and the greater part of the growth have the structure of a carcinoma composed of undifferentiated epithelial cells of an embryonic type.

Both innocent and malignant testicular teratomata are described, but it is doubtful if this distinction is justifiable. In some tumours the constituents may be of a more immature type than in others, and these tumours are usually highly malignant. But dissemination and a fairly rapid growth may be associated with histologically innocent tumours in which the cells are well differentiated. Again, the histology of individual tumours may vary in different parts, so it is wise to regard every

testicular teratoma as potentially malignant. Dissemination may be delayed or it may occur quite early; and metastases may be mixed or limited to one type of cell.

The origin of the teratomata is a matter of speculation. The most probable explanation of the sacrococcygeal and cranial tumours would seem to lie in an excessive or reduplicated growth of the germinal area, with the production of an imperfect second

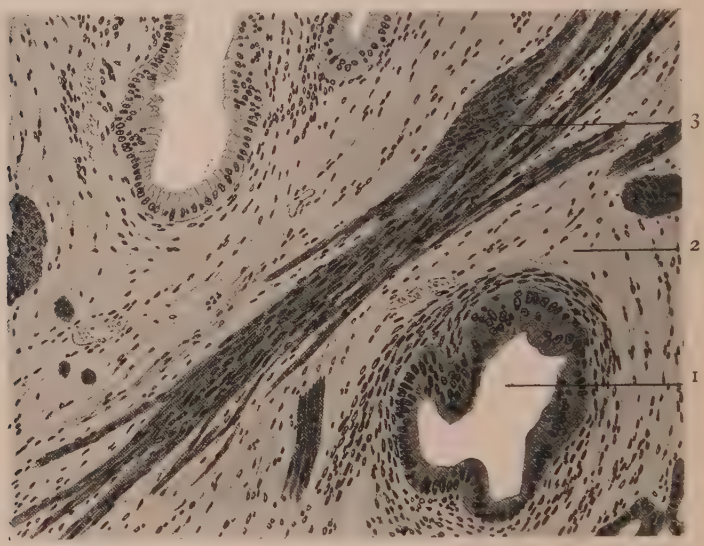

FIG. 115.—Microscopic section of a teratoma of the testicle. (1) Tubule lined by columnar epithelium and surrounded by condensed stroma; (2) loose connective tissue; (3) bundles of smooth muscle fibres.
Obj. 8 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

fœtus. Other forms may be accounted for by the theory of dislocated blastomeres. It is supposed that at a very early stage of development, blastomeres, the cells formed by the segmentation of the ovum, may become displaced, and so arrested in their growth. Later, they become active, with the production of cells of all three primitive layers.

The ovarian and testicular teratomata have also been ascribed to a process of parthenogenesis or development of an ovum or spermatozoon, or their precursors, the oocyte or spermatocyte, without fertilisation.

II. Teratoblastomata

This group includes the "mixed" tumours that are found in several situations, but chiefly in the kidney and the salivary glands. These tumours occur in their most characteristic form in the kidney, and have been described under many different names —carcinoma sarcomatodes, sarcoma of infancy, adenosarcoma, and rhabdomyosarcoma.

The majority of renal teratoblastomata occur in infancy or before the end of the second year. They form large rounded

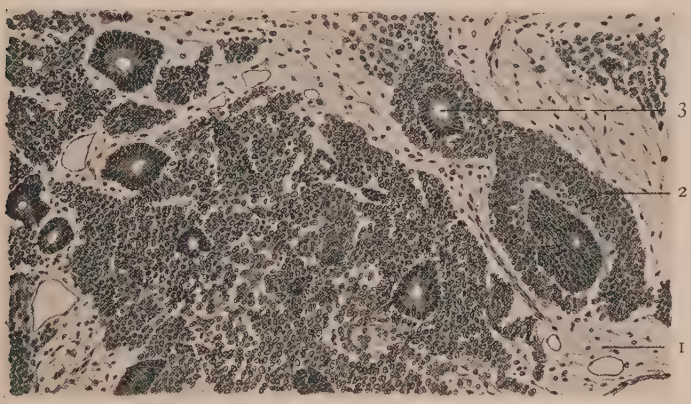

Fig. 116.—Microscopic section of a teratoblastoma of the kidney. (1) Loose oedematous stroma; (2) groups of indifferent sarcomatous cells enclosing (3) epithelial tubules.
Obj. 8 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

tumours which apparently grow from the pelvis, for the cortex of the kidney is often spread out over them in a thin layer. They are of a moderately firm consistence, and of a whitish appearance.

Sometimes they exhibit areas of hæmorrhage, and there is nearly always a considerable degree of mucoid degeneration. Their *microscopic* structure is highly characteristic. The main mass of the tumour is composed of small rounded or oval cells of a distinctly sarcomatous type, lying in a loose œdematous or mucoid connective tissue matrix. Intimately mingled with these cells are tubules lined by columnar cells, and these epithelial elements may be present in great numbers (Fig. 116).

More rarely, islands of cartilage and smooth and striated muscle fibres can be distinguished, but there is never any orderly

grouping or arrangement of the different constituents such as is seen in the true teratomata. The tumours are highly malignant, infiltrating locally and forming metastases.

Similar tumours, but of an even greater complexity, occur in the parotid and submaxillary glands and in other situations; they are, however, great rarities.

With regard to the origin of the teratoblastomata, the most commonly accepted theory is that of Wilms. The complicated structure of the growth makes it quite obvious that the source must be sought for far back in the developmental history of the individual, and Wilms traces it to a mesoblastic rest. The myotome, or primitive segment of the body, gives rise to the kidney anlage and also to the different connective tissues of the body wall, striated muscle, bone and cartilage, and it is supposed that cells of the myotome, displaced and arrested in their growth, may later be the starting-point of the tumours in question. A similar origin must be attributed to these growths in the salivary glands and elsewhere.

Powell White has described these tumours as Blastocytomata, for he regards them as being derived from indifferent cells or blastomeres, which are capable of giving rise to epithelial and mesoblastic elements. He believes it possible to trace all the stages in the direct transition of the sarcomatous cells into those of the epithelial type.

III. Heterochthonous Blastomata (Chorionepithelioma)

This tumour is of very great interest, possessing as it does features which single it out from all other neoplasms. It originates in the cells of another individual, and is in this sense a teratoma; but it is composed of cells, not tissues or organs, and is therefore a cytoma. It is, in fact, only to be compared to the heterochthonous blastomata with which we are familiar as artificial productions in the experimental propagation of tumours in the lower animals.

The chorionepithelioma is derived from the trophoblastic epithelium of the fœtus, and consequently is associated with pregnancy. It may occur during the course of, or after, a normal pregnancy, but more often it follows an abortion, and a high proportion of cases have been preceded by a hydatidiform mole. It is noteworthy that the incidence of the tumours rises in proportion to the number of previous pregnancies; the mother

of five children is more likely to suffer than a woman who has borne but one or two.

The primary growth may be situated in the uterus where it forms a polypoid fleshy mass, in the vagina, in the Fallopian tube, or in the ovary; it is an extremely hæmorrhagic growth, consisting mostly of blood clot enclosed in a thin irregular shell of paler tumour tissue. Dissemination takes place with great rapidity by the blood stream; the earlier and more numerous deposits are found in the lung and the liver, but any other part of the body may be affected.

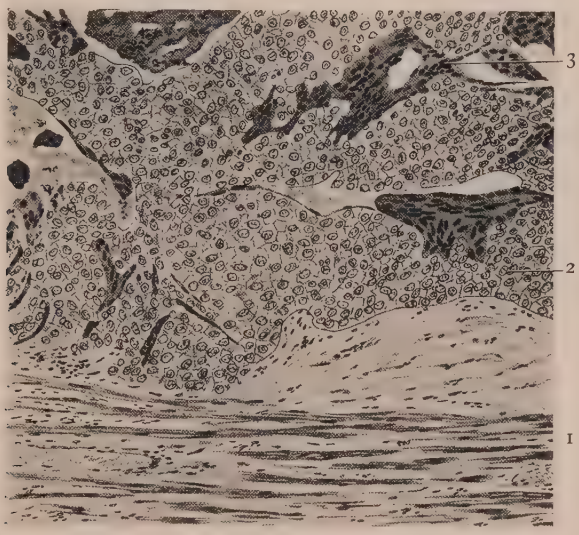

FIG. 117.—Microscopic section of a chorionepithelioma of the uterus. (1) Muscular tissue of the uterine wall; (2) Langhan's cells; (3) syncytium. Obj. 16 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

The chorionepithelioma of pregnancy is itself an uncommon phenomenon; still rarer are the instances of its development apart from childbearing. Cases have been recorded, however, in which it has appeared in teratomata of the testicle, the ovary, and the thorax. The importance of these observations will be referred to later.

The chorionepithelioma is one of the most fatal of all malignant growths, but some most remarkable examples have been established of spontaneous disappearance of the tumours and complete recovery.

The *histology* of the tumour is quite distinctive, though it is often obscured by hæmorrhages and degenerative changes.

Its cells are of two main types, corresponding as we now know to the Langhan's cells and the syncytium of the chorionic villi (Fig. 117).

The Langhan's cells are polygonal or cuboidal in shape, and have a clear vesicular cytoplasm; their nuclei are relatively large, possessing a well-marked chromatin network and nucleolus; they multiply by indirect division.

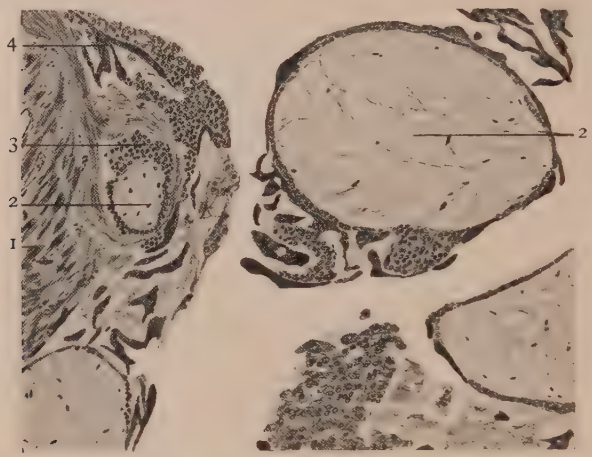

FIG. 118.—Microscopic section of chorionepithelioma of the uterus.
(1) Uterine wall; (2) chorionic villi; (3) Langhan's cells; (4) syncytium.
Obj. 16 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

The syncytial elements consist of large masses of dense protoplasm containing several very deeply staining oval nuclei. Frequently the protoplasm is drawn out into long narrow processes resembling endothelium. In the larger masses there may be vacuoles filled with fluid blood.

The two constituents may be mingled together, but more commonly the syncytium lies at the periphery of the closely packed masses of Langhan's cells.

The tumour has no stroma of its own, and has therefore no true structure, though it may be moulded into an irregular form from its mode of growth along the vascular channels of the normal tissues. It possesses no blood vessels, but derives a precarious nourishment from the circulating blood of the host;

for this reason its cells are unusually liable to undergo degenerative changes. It grows freely in blood vessels, distending and eroding them, and this peculiarity offers an obvious explanation of its rapid dissemination and its universally hæmorrhagic nature.

The character of the chorionepithelioma is so well established that it is not easy to appreciate how doubts could have been entertained as to its origin. Nevertheless, for some years the tumour gave rise to acute controversy. Even when its association with pregnancy was recognised it was supposed to be derived from the uterus, as the old name, deciduoma malignum, implies.

As a matter of fact, in no other malignant growth can we trace so clearly the stages in the transition from the normal. From the chorionic villus to the typical chorionepithelioma the chain is complete through the simple hydatidiform mole, the perforating or malignant hydatidiform mole, and the chorionepithelioma in which occur undoubted, though atypical, chorionic villi (Fig. 118). The evidence was rendered complete by the recognition of its occurrence in such undeniably fœtal tumours as the testicular and other teratomata to which reference has already been made.

PART III

THE SPECIAL PATHOLOGY OF TUMOURS

THE SKIN AND SUBCUTANEOUS TISSUES

By virtue of their accessibility, the tumours of the skin form eminently suitable objects for clinical and pathological study, while from their variety they offer a rich field for investigation. The subject is a difficult one, for there also occur in the skin a number of hyperplastic processes and congenital formations which closely simulate true blastomata ; and, added to these natural sources of confusion, we have others arising from a tendency on the part of some authors to an exaggeration of minor differences in growths of the same character.

Though to the dermatologist such fine discriminations have, no doubt, a clinical significance, to the general pathologist they seem a regrettable elaboration of an already complex subject.

Innocent Tumours.—***Fibromata*** are not very common, though blastomatoid overgrowths of fibrous tissue, both localised and diffuse, are not infrequently seen ; such well-known conditions as ***cheloid*** and ***molluscum fibrosum*** may be quoted as examples of blastomatoid fibromatoses (p. 76). The true fibromata form hard rounded tumours, often multiple, and occasionally of some considerable size. ***Lipomata*** are common in the subcutaneous tissues ; they form smooth lobulated tumours of a somewhat darker colour than the surrounding fat. Sometimes the tumours contain so much fibrous tissue as to warrant their being named ***fibrolipomata.*** ***Leiomyomata*** are occasionally seen as small tumours, often multiple, arising from the arrectores pilorum. A condition of myomatosis in connection with the walls of arterioles is sometimes seen.

True ***neuromata*** and ***myxomata*** are extremely rare, though

they have been described. ***Hæmangeiomata*** and ***lymphangeiomata*** are of frequent occurrence in the skin and subcutaneous tissue; as I have already pointed out (p. 171), the majority of them are congenital blastomatoid processes, and not true tumours. In some cases there is a simultaneous hyperplasia of the fibrous tissue, resulting in the production of the ***fibro-angeioma.***

Solid and cystic epithelial tumours may grow from the surface epithelium, the hair follicles, the sebaceous glands, and the sweat glands, though blastomatoid conditions are far more numerous than true blastomata.

An undoubted ***papilloma*** of the surface epithelium may be seen, though it is not particularly common, but multiple ***warts*** and ***condylomata,*** presumably infective in origin, are very frequent.

Molluscum contagiosum is another blastomatoid condition which in all probability should be regarded as an infective process. The tumours are usually multiple, forming small rounded nodules immediately beneath the epidermis; they often show slight umbilication. They consist of solid alveoli of epithelial cells separated from one another by processes of connective tissue, and arranged around a central point. The innermost cells exhibit an anomalous keratinisation, the individual degenerated cells being known as "molluscum bodies," and the centre of the tumours is occupied by soft, completely degenerated cell debris (Fig. 119).

Simple ***adenomata*** of the surface epithelium are occasionally seen. They consist of solid masses and trabeculæ of epithelial cells embedded in a fibrous stroma. Sometimes the central cells are keratinised, but more often they undergo necrosis so that pseudocysts are formed, when the tumour is known by the name of ***epithelioma adenoides cysticum.***

A simple ***epidermal cyst,*** usually an "inclusion cyst," may be encountered; it consists of a mass of keratinised material surrounded by a narrow zone of active, healthy epithelial cells. Cystic tumours also arise from the sebaceous and sweat glands. The commonest example is the simple sebaceous cyst, but multilocular, even papilliferous, cysts may grow from the sweat glands. Both sebaceous and sweat glands are liable to hyperplastic processes, but true adenomata also occur apart from these conditions.

In the ***sweat gland adenoma*** the structure is usually that of groups of irregular elongated acini, and the appearance is not unlike that of a mammary fibro-adenoma. The epithelium

lining the acini is of a low columnar form, and a reversion to squamous cells may take place. In the ***sebaceous gland adenoma*** the characteristic cells are grouped together in solid alveoli, which may show a certain amount of central necrosis or calcareous infiltration.

FIG. 119.—Molluscum contagiosum. (1) Surface epithelium, (2) masses of epithelium showing (3) molluscum bodies and (4) central keratinisation. Obj. 16 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

Malignant Tumours.—***Sarcomata.***—Primary sarcomata of the skin are somewhat rare. One of the commonest forms is a slowly growing spindle-celled or fibro-sarcoma; large round-celled alveolar sarcomata and polymorphic-celled sarcomata are also met with, and are of a much higher grade of malignancy.

An extremely interesting condition of great rarity is seen in the primary multiple sarcomata of the skin. Several types of this disease are described, but the commonest appears to consist in the formation of somewhat soft tumours of a moderate size, over which the epidermis is stretched and of a pinkish colour. Microscopically, the tumours have the structure of a small round-celled sarcoma.

Endotheliomata.—The commonest tumour of an endotheliomatous nature occurring in the integument is the ***hæmangeioma simplex*** (p. 171). This is usually innocent, but it may exhibit an infiltrative growth and become definitely malignant. Comparable tumours derived from lymphatic endothelium may

sometimes be encountered. A multiple angeiosarcoma of the skin is described, which should probably be placed among the endotheliomata. Anomalous tumours, generally classed among the carcinomata, occasionally occur, and some authorities believe that these are derived from endothelium.

Melanomata.—These tumours have been dealt with in a previous section (p. 191).

The majority of congenital pigmented moles are, of course, entirely innocent, but they may assume malignant characters and disseminate with appalling rapidity, both by the blood stream and the lymphatic system. Occasionally melanomata may arise independently of congenital moles.

Histologically, the tumours fall into two main divisions according to whether their structure is that of a carcinoma or a sarcoma ; but while their nature is still in dispute, it would seem more satisfactory to class all forms under one name than to attempt a division, which may eventually prove to be without justification, into melanocarcinomata and melanosarcomata.

Carcinomata.—It is particularly in respect to the malignant epithelial neoplasms of the skin that confusion has resulted from unnecessary elaboration in our classifications. The skin is a highly complex structure, and the numerous carcinomata which grow from the surface epithelium and its derivatives may very naturally exhibit considerable variations from one another. But, unless it is distinctly advantageous from the clinical standpoint, a separation of several distinct forms of tumour growth based on such minor differences would scarcely seem to be justifiable.

The squamous-celled carcinoma is a very common tumour of the skin ; it may be of the papillary or the infiltrating type, and it is frequently ulcerated. It presents all the distinguishing features of this type of carcinoma (p. 143).

Anomalous histological forms are sometimes met with in which there is an alteration into the adenomatous type. Some of these are obviously derived from sweat glands, but in others it is impossible to distinguish their points of origin. A carcinoma derived from sebaceous glands may reproduce the normal structure of the gland with great fidelity, but it may form a simple alveolar or even a squamous-celled tumour.

The degree of malignancy possessed by different squamous-celled carcinomata is very variable. They all cause local destruction of tissue, but they do not by any means exhibit a constant

rapidity of growth, nor do they all form metastases. For the most part distant metastases are rare, and there is seldom any extension except to the neighbouring glands, but occasionally a case is seen in which dissemination is more widespread.

The importance of chronic irritation as a factor in the causation of cancer is very marked in the carcinomata of the skin. The cancer in the scrotum of sweeps, due to the constant irritation of soot, the cutaneous cancer of paraffin workers, the X-ray and the Kangri cancers are all obvious examples, and many others might be quoted.

Rodent Ulcer.—This tumour has features which bring it into a class apart from the ordinary squamous-celled carcinoma (p. 146). It occurs as a rule on the face, at the angles of the nose and the eyes, and on the forehead, but extra-facial forms are occasionally seen. Its growth is infiltrative but slow; the facial tumours never form metastases, though these may occur in the extra-facial ones.

Secondary Tumours.—Carcinomata and sarcomata may both give rise to metastases in the skin, though not very often. In mammary carcinomata, however, cutaneous metastases are frequently seen as the result of permeation of the superficial lymphatics. Apart from permeation, the skin may be directly invaded by underlying malignant connective tissue and epithelial tumours, and nodules occasionally form from the lodgment of vascular emboli.

MUSCLES AND FASCIÆ, TENDONS AND BURSÆ

Though new growths of the muscular constituents of various organs are not uncommon, tumours of muscles themselves are rare, and are usually derived from the fasciæ and connective tissue septa. Tumours of tendons and bursæ are even less conmmon.

Innocent Tumours.—***Fibromata*** are probably the commonest tumours; they may grow from the connective tissue of muscles, and may also be met with in tendon sheaths; they are rather liable to undergo myxomatous degeneration. A peculiarly hard fibroma, known as a ***"desmoid,"*** grows from the sheath of the rectus abdominis muscle.

Lipomata are met with in the substance of muscles and also in connection with their sheaths, and a papillomatous fatty tumour, the ***lipoma arborescens,*** may occasionally be encountered on the inner surface of tendon sheaths.

Hæmangeiomata and ***lymphangeiomata*** are occasionally seen in muscles, and a diffuse hæmangeioma simplex may grow in the walls of bursæ ; all these formations are probably blastomatoid in nature.

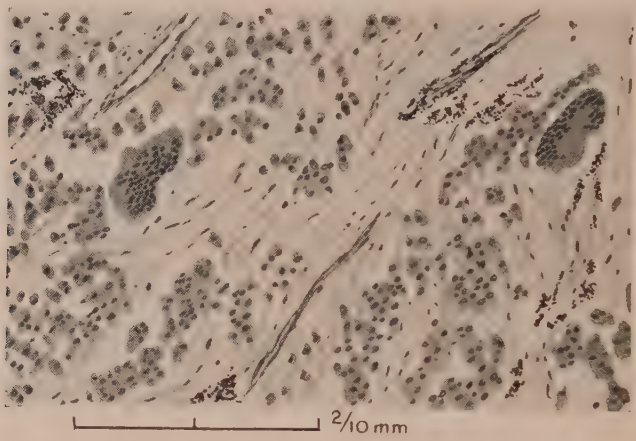

Fig. 120.—Section of a " myeloid-sarcoma " of a tendon sheath.

Osteomata are very rare, though metaplastic ossification is not uncommon in both muscles and tendons. A true osteoma, however, may grow in muscles and is supposed to be derived from cells which have become displaced from the deep surface of the periosteum of a neighbouring bone.

Rhabdomyomata have been described, but are extremely uncommon ; they are probably congenital tumours, growing from " rests " of embryonic muscle cells.

Endotheliomata containing giant cells of the " myeloid-sarcoma " type occasionally develop in tendon sheaths (Fig. 120).

Malignant Tumours.—***Sarcomata*** are not uncommon in connection with muscles, though they appear to originate in the fascia and connective tissue septa rather than in the muscle fibres themselves. Round- and spindle-celled forms occur, but the commonest type is a slowly growing fibrosarcoma which exhibits a marked tendency to myxomatous degeneration.

Fibrosarcomata are very occasionally found growing from tendons and bursæ.

Endotheliomata.—Malignant tumours derived from endothelial cells may develop in the substance of muscles, but are very rare.

Carcinomata are always secondary.

Secondary Tumours.—Carcinomata often extend to muscles directly, but very seldom produce distant metastases in them. Sarcomata also invade muscles by direct extension, and in some highly malignant round-celled tumours distant dissemination may take place.

THE BONES

Innocent Tumours.—***Osteomata.***—In a previous section (p. 84) I have drawn attention to the difficulty that exists in distinguishing between the various conditions of bony hyperplasia and the true osseous neoplasms, and there is no necessity to dwell upon the subject again. But it must be clearly understood that when we talk of osteomata, and of other tumours of bones, we are probably including many blastomatoid growths.

Osteomata grow from the periosteal or the medullary surfaces of bones as indolent, rounded, or lobulated tumours composed of compact or cancellous bone; they are often multiple.

The compact ivory osteomata are chiefly found in connection with the bones of the skull. They are not uncommon in the external auditory meatus or the nose, and may give rise to complete obstruction of the passages concerned; while if they happen to arise in the orbit, they may displace and destroy the eyeball.

Fig. 121.—Tibia and fibula showing multiple exostoses.

The cancellous osteomata occur for the most part in the long bones. An important clinical variety is the ***"cartilaginous exostosis"*** (Fig. 121). These tumours appear as a rule in young people, and are frequently multiple. In some cases there seems

to be a distinct hereditary factor in their formation. They often have a constricted base which gives them a characteristic "mushroom" shape, and they are covered with a layer of hyaline cartilage. From the fact that their growth generally ceases when the full development of the skeleton is attained, there can be no doubt that they are really blastomatoid in nature; while their common situation at the epiphyseal extremity of the bones suggests that they are derived from areas of cartilage which have become displaced during development.

FIG. 122.—Massive chondroma of the lower end of the femur.

Chondromata are divided into ecchondromata and enchondromata according to whether they develop on the surface or in the interior of bones. Like the osteomata, they are often multiple and have a tendency to occur in families. In many cases they appear to be derived from islands of cartilage which have become displaced during the development of the bone, and they usually develop at the ends of the long bones, and in the bones of the hands and feet.

Chondromata form irregular lobulated tumours, having a

characteristic cartilaginous appearance on section. They are generally enclosed in a fibrous capsule, from the deep surface of which trabeculæ pass in between the lobules (Fig. 122). Retrograde changes are common in chondromata; myxomatous degeneration is frequently seen, and they often become infiltrated with calcium salts. Sometimes true bony metaplasia occurs, and it is probable that many of the multiple osteomata are examples of ossifying chondromata. But the most important secondary change is the transition of some part of the tumour into a malignant growth, a chondrosarcoma.

Fibromata may grow from the periosteum or in the medullary cavity. They may form firm hard tumours which often show a certain amount of ossification; or they may be vascular and highly cellular, when it becomes difficult to separate them from the fibrosarcomata. The softer tumours are liable to exhibit myxomatous degeneration.

Myxomata, lipomata, and ***angeiomata*** are rare tumours which may occur in the substance or on the surface of bones.

Myeloid Sarcomata (p. 86) may be classed among the innocent tumours of bones, though they have a certain activity of growth, and give rise to a considerable destruction of the normal tissues.

Myelomata have been referred to elsewhere. Inasmuch as they are derived from the marrow they do not really belong to the tumours of bone, but they may be mentioned here for the sake of convenience.

Malignant Tumours.—The primary malignant tumours of bone are all of the connective-tissue group; carcinomata are invariably secondary.

Sarcomata.—A bewildering variety of sarcomata grow in connection with the bones, practically every type being represented. The tumours may start in the medullary cavity or from the periosteum; they may be of the simple undifferentiated variety, or they may form bone, cartilage, or fibrous tissue.

The central sarcomata are mostly of the round-, spindle-, or polymorphic-celled type, the latter frequently containing many giant cells and being difficult to distinguish microscopically from the myeloid sarcomata. They usually start in the cancellous tissue at the ends of the long bones, and give rise to much absorption of the compact layer. They spread along the medullary cavity, and eventually pass through the Haversian canals to the periosteum.

Occasionally the central sarcomata produce fibrous tissue, cartilage, or bone, and these forms are not very malignant; but the round-celled tumour is one of the most deadly of all new growths, and disseminates with the greatest rapidity.

Fig. 123.—Sub-periosteal osteosarcoma of the femur which has invaded the medullary cavity. There is much bone formation, and bone spicules can be seen radiating out from the shaft (cp. Fig. 124).

The periosteal sarcomata may be of the round-, spindle-, or giant-celled type, or they may be more slowly growing fibro, chondro, or osteosarcomata. The soft tumours, especially the round-celled sarcomata, are extremely malignant. They form small oval or rounded tumours, and give rise to a certain amount of erosion of the underlying bone, but general dissemination takes place so early that there is seldom time for a large local development of the growth to take place. These tumours are frequently very vascular, and may show advanced myxomatous degeneration.

The more highly differentiated tumours grow with less rapidity. They tend to envelop the bone, gradually spreading along its surface, and they also grow into and invade the medullary cavity (Fig. 123). In the osteo, or ossifying, sarcoma there is a formation of true bone, spicules of which radiate out from the surface of the bone into the substance of the growth (Fig. 124). In another type, the osteoid sarcoma, trabeculæ are laid down, but do not become calcified. Similarly, chondrosarcomata in all degrees of differentiation may be encountered.

Endotheliomata.—Certain of the malignant periosteal

growths are sometimes regarded as being of endothelial origin, and there occurs in the medullary cavity of the long bones a malignant hæmangeioma (p. 176).

Secondary Tumours.—In certain forms of carcinomata metastases are very commonly found in the bones, chiefly the vertebræ,

Fig. 124.—Macerated specimen of an osteosarcoma of the lower end of the femur, showing the formation of bone.

the ribs and sternum, the femur, the humerus, and the bones of the skull. This is especially the case in carcinomata of the breast, the prostate, and the thyroid. Another form of tumour which may give rise to bony deposits is the malignant hypernephroma.

Invasion of the bone may be the result of vascular embolism, lymphatic permeation, or the direct extension of the primary growth or its metastases. The metastases may be situated on the surface or in the cavity of the bone; in the latter position

they give rise to gradual absorption of the compact tissue, and the first indication of their presence may be the occurrence of a spontaneous fracture.

Secondary sarcomata of bone are much less common, but the round-celled tumours are liable to form deposits in the skull bones, and the skeleton may be extensively invaded in generalised melanotic sarcoma.

THE CIRCULATORY SYSTEM

THE HEART AND PERICARDIUM

Primary cardiac tumours are extremely rare. Among the benign neoplasms, ***fibromata*** and ***lipomata*** are described as growing from the pericardium and the wall of the heart itself; in the latter situation the tumours usually form polypoid masses beneath the endocardium. Two interesting tumours, probably congenital in origin, that have been recorded as occurring in the myocardium are the ***rhabdomyoma*** and the ***myxoma.***

Primary malignant tumours are also very uncommon. An ***endothelioma*** is said to occur in the pericardium, and ***sarcomata*** may be met with in the heart wall.

Secondary Tumours are more often seen. The pericardium may be directly invaded by intrathoracic and mammary tumours, and both it and the heart may present metastatic growths, though, as a rule, only in advanced cases of malignant disease. The commonest secondary tumour is probably the melanotic sarcoma, and I have also noticed on more than one occasion, in cases of advanced mammary carcinoma, small metastases along the course of the coronary arteries.

THE BLOOD AND LYMPH VESSELS

Primary blastomata are practically unknown in the larger vessels, though a ***myomatosis*** may be encountered in connection with the walls of the smaller arteries and veins.

From the capillaries originate the various forms of ***angeiomata*** (p. 170), and the ***endotheliomata*** are derived from the lining cells of both blood and lymph capillaries. Under the name ***perithelioma*** some authors include a special class of endothelioma derived from perivascular lymphatics.

Secondary Growths.—The role of the vascular and lymphatic channels in the dissemination of malignant growths has already been fully discussed (p. *27 et seq.*).

THE LYMPHATIC GLANDS

The neoplasms of lymphadenoid tissue have been considered in Part II. (p. 92). A true benign blastoma of lymphatic glands

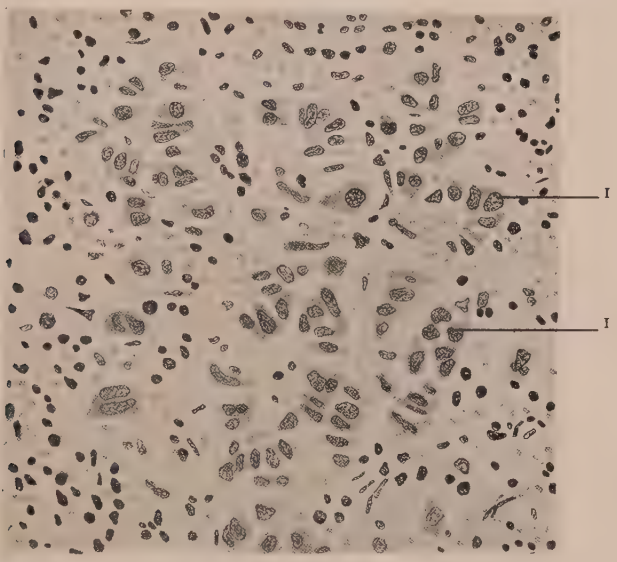

FIG. 125.—Microscopic section of a spleen showing diffuse malignant infiltration, secondary to carcinoma of the breast. (1) Carcinoma cells.
Obj. 3 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

is practically unknown, but primary malignant tumours are not infrequent. The commonest variety is the ***lymphosarcoma*** (p. 116), but ***fibro, angeio,*** and ***endothelial sarcomata*** may also occur.

A small ***round-celled sarcoma*** originating in a lymphatic gland may be mistaken for a lymphosarcoma. It is, of course, a much more malignant growth, infiltrating the capsule of the gland and forming distant metastases; moreover, it possesses no fibrous tissue reticulum.

Secondary Growths occur earlier and with greater frequency in the lymph glands than in any other organ of the body, and

it is no exaggeration to say that an accurate knowledge of the lymphatic system is the key to the successful surgical treatment of malignant disease. The carcinomata, of course, almost invariably form metastases in lymph glands; sarcomata, contrary to the generally accepted teaching, very frequently do the same, though in these tumours dissemination by venous channels is often of greater importance.

THE SPLEEN

Primary neoplasms of any kind are comparatively rare in the spleen. ***Fibromata*** and ***lymphangeiomata*** may occur, but ***lympho-***, and ***spindle-***, and ***round-celled sarcomata*** are probably more common.

Secondary Tumours.—It is curious to note the relative immunity of the spleen to secondary growths. The organ may be invaded by direct extension from an adjacent organ, or by secondary deposits in the glands in the hilum, but true metastatic tumours are uncommonly rare. I have, however, described an interesting form of diffuse malignant infiltration of the spleen, unaccompanied by any macroscopic evidence of the condition, as occurring in cases of carcinoma of the breast (Fig. 125, and p. 32).

THE RESPIRATORY SYSTEM

THE NOSE

Innocent Tumours.—Quite the commonest tumour is the ***nasal polyp,*** but only occasionally can this be regarded as a true neoplasm. In the majority of cases it represents merely a localised hypertrophy of the mucous membrane, and is composed of loose, œdematous connective tissue, covered with a layer of epithelium and often containing a few gland tubules. Sometimes the polypi appear to be of inflammatory origin, consisting of œdematous fibrous tissue, fairly rich in cells, and containing many delicate capillary vessels, around which are small collections of mononuclear leucocytes. However, true polypoid ***adenomata*** and ***fibromata*** do occur, though not often. Other innocent tumours are ***papillomata***, ***osteomata,*** and ***chondromata.***

Malignant Tumours.—***Sarcomata*** may occur primarily in the nose or in the accessory sinuses. Round- and spindle-celled and lymphosarcomata are the usual forms, and a chondrosarcoma may occasionally be seen.

Carcinomata are quite uncommon. They may be either of an atypical squamous-celled, or an adenocarcinomatous type.

THE LARYNX

Innocent Tumours.—Innocent tumours of the larynx are of unusual importance, for, from their situation, they may give rise to serious respiratory embarrassment as well as aphonia. Simple ***papillomata*** are the commonest tumours, the next in order of frequency being the ***fibromata. Lipomata, myxomata, angeiomata, chondromata,*** and ***adenomata*** have all been recorded as occurring in the larynx, but have very little practical importance.

Fig. 126.—Larynx and trachea opened from behind to show multiple papillomata.

Papillomata occur as localised or diffuse warty growths, usually springing from the vocal cords (Fig. 126). They are composed of connective-tissue processes covered with an hypertrophied squamous epithelium, and many of them are undoubtedly of inflammatory origin. They tend to recur after removal, but seldom assume true malignant characters. ***Fibromata*** may be sessile

or pedunculated, and they also arise as a rule from the cords.

Malignant Tumours.—***Sarcomata*** are rare. They are usually of the round- or spindle-celled variety, though fibro and chondrosarcomata also occur.

Endotheliomata have been described, but are uncommon.

Carcinomata are by no means infrequently seen, growing from the cords or the mucous membrane below them, the epiglottis, or the pyriform fossæ. They usually form papillomatous or warty tumours, and are almost invariably of the squamous-celled type, though adenocarcinomata, and a scirrhous carcinoma simplex have also been recorded.

As a rule, laryngeal carcinomata remain fairly well localised to the throat and the cervical glands, but very occasionally they may form distant metastases.

THE LUNGS AND BRONCHI

Primary tumours of the air passages are very rare indeed, but polypoid ***fibromata*** and ***sarcomata*** may be encountered, and ***carcinomata,*** usually columnar-celled adenocarcinomata, but occasionally of the squamous-celled type, may grow from the bronchial mucous membrane or the peribronchial mucous glands.

Primary tumours of the lungs are also extremely rare. ***Fibromata, chondromata,*** and ***osteomata*** are sometimes seen, though most of the bony and fibrous tumours encountered are probably inflammatory in origin. An ***adenoma*** of the lung is almost unknown in the human being, though it is fairly common in the mouse. ***Teratomata*** originating in the thoracic cavity may invade the lung, but it is doubtful if they are ever primary in that organ.

Sarcomata.—Round-, spindle-, and polymorphic-celled sarcomata may occur, and chondrosarcomata may grow from the cartilages of the bronchial walls.

Carcinomata may arise from the lining epithelium or the mucous glands of the bronchioles, and from the alveolar epithelium.

Bronchial carcinomata are usually columnar-celled growths, and the cells may even be ciliated ; the alveolar carcinomata are commonly of an atypical squamous-celled type. Pulmonary carcinomata often form metastases in the brain, and the

cerebral symptoms caused thereby may even dominate the clinical picture.

Secondary Growths.—Pulmonary metastases are of frequent occurrence in all forms of malignant disease, developing from vascular emboli or from the permeation of the subpleural and peribronchial lymphatics.

Vascular dissemination is more common in sarcomata than in carcinomata, and is specially well seen in chorionepithelioma. In my own experience I have found that carcinomata more often invade the lungs by the lymphatic channels than by the blood stream, and this method of spread may be seen very clearly in the case of mammary tumours.

THE ALIMENTARY SYSTEM

THE LIPS

Innocent tumours of the lips are rarely of any importance, but angeiomata are not uncommon in childhood.

The ***vascular nævus,*** or ***capillary angeioma,*** may grow on the mucous or the cutaneous surface ; it is a congenital tumour, though it may be quite small at birth. The condition of congenital hypertrophy of the lip, known as ***macrocheilia,*** is due to a ***cavernous lymphangeioma.***

Malignant Tumours.—The ***squamous-celled carcinoma*** is a fairly common tumour in men over forty years of age ; it is rare in women. It is usually associated with some form of chronic irritation, and is especially liable to appear in smokers who are in the habit of using a clay pipe. In untreated cases the growth extends locally to the jaw, and instances are recorded of infection of the other lip from direct contact ; metastases also form in the submaxillary and submental lymph glands, but there is seldom any widespread dissemination.

Endotheliomata may occasionally be met with.

THE TONGUE

Innocent Tumours.—The innocent connective-tissue tumours are not often seen, but ***fibromata, lipomata, angeiomata*** and ***myxomata*** may occur, usually early in life. ***Macroglossia,*** or

congenital hypertrophy of the tongue, is caused by a ***cavernous lymphangeioma.***

The innocent ***squamous papilloma*** is less common than the malignant epithelial growths, and is always to be regarded with suspicion.

Dermoid cysts are sometimes encountered in the middle line of the floor of the mouth.

A rare tumour is one derived from remnants of the ***thyro-glossal duct.*** It is situated in the base of the tongue, and is usually cystic.

Malignant Tumours.—***Sarcomata*** are not very common. They are of the round-celled and lymphosarcoma type, and a very careful microscopic examination may be necessary to distinguish them from conditions of chronic inflammation.

The ***squamous-celled carcinoma*** is the commonest of all the tumours of the tongue. It most often occurs in men between forty and sixty years of age, and may be of the ulcerative, papillomatous, or nodular type. The growth very frequently follows on prolonged irritation from a jagged tooth or a pipe stem, or it may be preceded by a chronic superficial glossitis or a syphilitic leucoplakia. Lymphatic dissemination takes place early in the disease, the glands on both sides of the neck being involved.

It is comparatively rare for metastases to form in other parts of the body, and in forty-three consecutive autopsies on cases of advanced carcinoma of the tongue and mouth I found secondary growths only four times in the lungs, twice in the liver, and once in the stomach, axillary, and tracheobronchial glands. There is, however, widespread local extension with ulceration, and the cervical metastases tend to break down and fungate, so that the last stage of the patient is pitiful in the extreme. Death usually results from septic absorption, broncho-pneumonia, or hæmorrhage from the cervical vessels. A point to be emphasised, one having an important bearing on the prognosis, is the difficulty there may be in demonstrating the cervical metastases in early cases. I have more than once made an extremely careful examination of the contents of the cervical triangles removed at the same time as the tongue, without success ; nevertheless, the patients have returned within a few months with large masses of growth in the neck.

THE MOUTH, PHARYNX, AND TONSILS

The ***squamous-celled carcinoma*** may grow in any part of the mouth. When situated in the posterior part, it usually involves the fauces and tonsils.

A true ***teratoma*** occurs in the vault of the pharynx.

The tonsil is liable to two forms of sarcomatous growth, the ***round-celled sarcoma*** and the ***lymphosarcoma.*** Other malignant connective-tissue tumours may occur in the mouth, but are rare.

THE JAWS

The innocent connective-tissue tumours are the ***fibromata, myxomata, osteomata,*** and ***chondromata;*** they are not common.

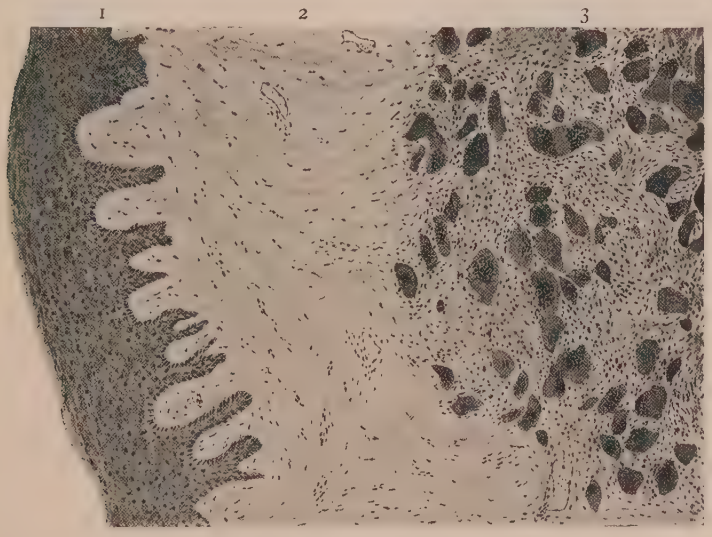

FIG. 127.—Microscopic section of a myeloid epulis of the jaw. (1) Surface epithelium; (2) sub-epithelial connective tissue; (3) tumour tissue consisting of giant cells embedded in a cellular stroma.

Obj. 16 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

The ***myeloid epulis,*** growing from the alveolar margin, has a certain degree of local malignancy. It is composed of a cellular connective-tissue stroma in which appear numerous giant cells of the osteoclast type (Fig. 127). It is to be distinguished from various chronic inflammatory formations.

A myeloid sarcoma occasionally develops in the interior of the lower jaw.

Different types of solid and cystic tumours may grow in connection with the teeth, the most important being one derived from the primitive enamel organ, the ***epithelial odontome.*** This forms a very dense, hard tumour which may grow to a considerable size. On section, it is seen to be composed of a

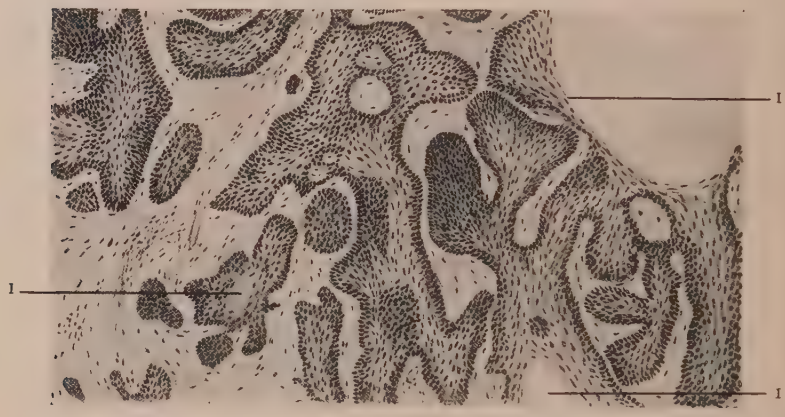

FIG. 128.—Microscopic section of an epithelial odontome of the lower jaw. The tumour is composed of branching columns of epithelial cells lying in a fibrous stroma. The inner cells of the columns are loosely packed together, and there is a tendency to the formation of cystic spaces (1).

Obj. 16 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

framework of dense fibrous tissue, which may be partly calcified, enclosing a collection of cystic spaces. *Microscopically*, the growth consists of broad, branching columns of cells surrounded by a dense fibrous stroma ; the outer cells are columnar in shape, but the inner ones become flattened, and there is a marked tendency to cystic degeneration (Fig. 128).

Malignant Tumours.—*Sarcomata* are rather more common in the upper jaw than the lower. They may be of the round- or spindle-celled type, or the more slowly-growing fibro, osteo, or chondrosarcomata.

The ***squamous-celled carcinoma*** grows from the alveolar surface, and a somewhat atypical example of this tumour occurs in the antrum of Highmore.

THE SALIVARY GLANDS

Innocent Tumours.—***Fibromata, myxomata, chondromata, rhabdomyomata,*** and ***angeiomata*** have been described, but it is probable that the majority of them are really instances of the predominant growth of a mixed tumour.

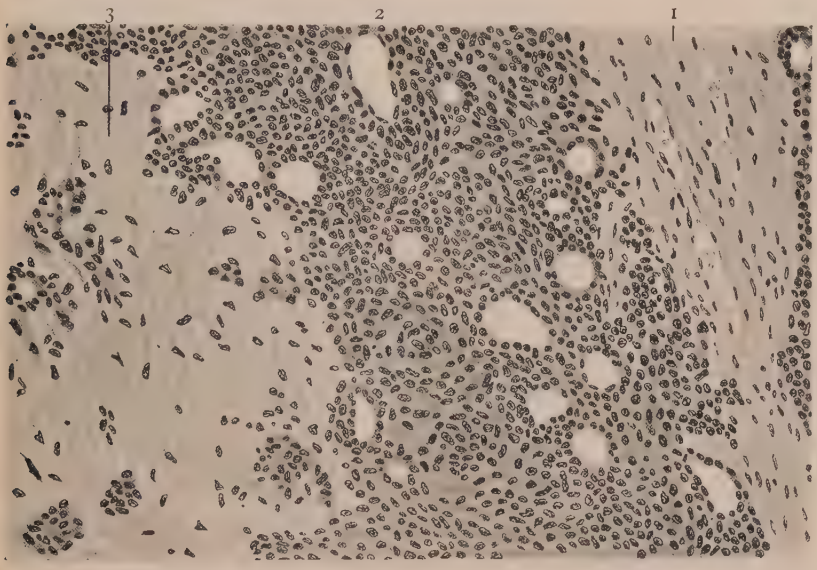

FIG. 129.—Microscopic section of an endothelioma of the submaxillary gland. (1) Connective tissue stroma; (2) dense mass of tumour cells showing the formation of irregular spaces; (3) area in which the growth has undergone myxomatous degeneration.

Obj. 8 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

The simple ***adenoma*** is so rare as to be little more than a possibility.

Malignant Tumours.—***Sarcomata*** are very uncommon and are, as a rule, highly malignant.

Carcinomata.—Adenocarcinomata and squamous-celled carcinomata do occur, though not often.

By far the commonest tumour of the salivary glands is the so-called ***parotid tumour,*** which, though it occurs chiefly in the parotiod gland, also grows in the submaxillary gland and occasionally in other situations. This tumour has given rise to a great deal of discussion, and it has been the fashion for many years to call it an endothelioma; but it is now pretty well agreed

that it is derived from epithelium, probably from the cells of the duct of the gland.

The parotid tumour forms a slowly growing, lobulated mass, which usually shows only a slight degree of malignancy. It may have been present for years, and have reached an enormous size, without showing any infiltrative growth and without forming metastases. Nevertheless, it frequently recurs after removal, since isolated lobules may escape notice at the operation.

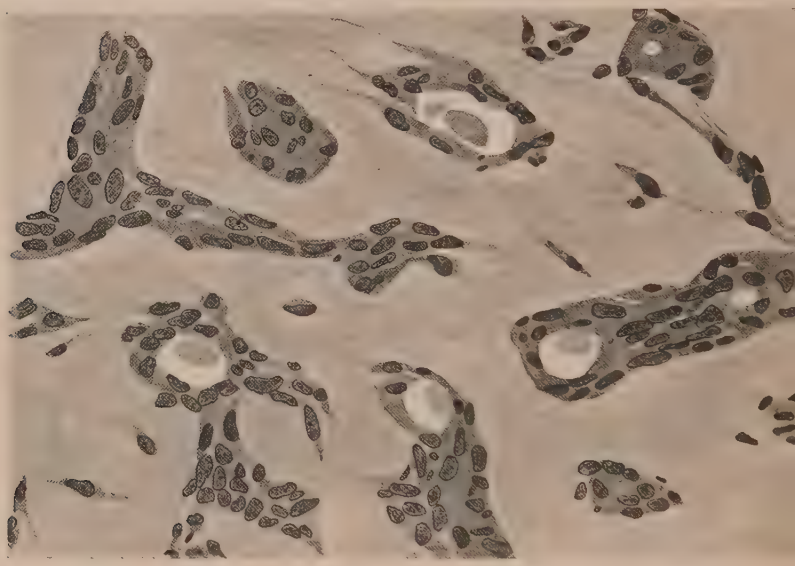

Fig. 130.—Microscopic section of an endothelioma of the parotid gland. The tumour is composed of myxomatous tissue in which lie groups of endothelial cells which often enclose distinct lumina.

Obj. 8 mm. apochrom. Comp. oc. 12. Tube length, 160 mm.

On section it is fairly firm, and has a semi-translucent surface, mottled with whitish areas of denser growth. Some tumours may be soft and gelatinous. *Microscopically* (Figs. 129 and 130) it is composed of groups of cells of a somewhat irregular form; some may be cubical, others are polygonal or flattened. These cells may occur in solid masses, or they may form narrow branching strands, and they frequently line spaces or lumina. Perfectly typical squamous epithelium with prickle cells and keratinisation is often present. A distinctive feature of the tumour is the fact that it tends to undergo extreme mucoid degeneration. The

condensed myxomatous stroma encloses isolated tumour cells which become loosened and separated from the main cell masses so that an appearance closely resembling that of cartilage is produced. True cartilage may be present in some tumours, and even bone, but it is probable that these growths belong to a different group and are really teratomata. Tumours having exactly the same histology as the parotid tumour occur occasionally on the scalp. In one of these I have seen not only cartilage but bone and marrow tissue. But I have not yet seen a parotid tumour in which the anomalous appearance of the stroma could not be explained in the way I have indicated.

THE ŒSOPHAGUS

Innocent Tumours.—Innocent tumours of the œsophagus are quite uncommon. ***Fibromata, myomata, lipomata, myxomata,*** and ***adenomata*** are described as occurring in the substance of the wall, or projecting as polypi into the lumen.

Malignant Tumours.—***Sarcomata*** are very rare; they are usually of the spindle-celled variety.

Carcinoma.—This is the commonest tumour in this region. It is usually of the squamous-celled type, though very occasionally an adenocarcinoma may arise from glands in the wall, or from misplaced islands of columnar epithelium.

Carcinomata of the œsophagus originate, for the most part, in one of three situations: at the level of the cricoid cartilage, at the level of the bifurcation of the trachea, or at the lower end. Most often the growth is soft and ulcerated, and though it encircles the lumen, no great mass of tissue is formed. Sometimes, however, it is more scirrhous in type, and gives rise to quite a large tumour. Distant metastases are not often seen, but the neighbouring lymphatic glands are involved. Ulceration into the trachea or bronchi, or into one or other of the pleural cavities is common, and a septic broncho-pneumonia or pleurisy is often the terminal event. I have also known a patient to die from hæmorrhage as the result of erosion of one of the intercostal branches of the aorta. In œsophageal carcinomata the patients are generally very emaciated from the mechanical interference with nutrition.

Dermoid cysts and true ***teratomata*** are occasionally found in the œsophagus, usually at its junction with the pharynx.

THE STOMACH

Innocent Tumours of the stomach are uncommon, and seldom have any clinical importance. ***Fibromata, myomata,*** and the compound ***fibromyomata*** form small nodular tumours in the substance of the wall; they may occasionally grow to a considerable size, and sometimes project as polypi into the lumen of the viscus.

FIG. 131.—Stomach opened to show a massive pyloric carcinoma (A).

Lipomata and ***lymphangeiomata*** are described as usually occurring under the serous coat. The ***adenomatous polyp*** is a rarity which may also be met with.

Malignant Tumours.—***Sarcomata*** are quite rare, but the round-, polymorphic-, and spindle-celled types occur, and a malignant myoma, or leiomyosarcoma, is described.

Carcinoma.—The gastric carcinoma occupies a highly important position among the malignant growths, for in England and Wales during the three years 1901-1903, out of a total number of 84,448 deaths from cancer, the primary tumour was in the stomach in 14,468 cases.

Carcinoma of the stomach is somewhat more common in men than in women, and usually appears after middle life. There is often a history pointing to previous ulceration, but many

Fig. 132.—Stomach laid open to show a fungating "cauliflower" carcinoma.

authorities deny that there is any connection between the two conditions. The majority of the tumours are situated in the regions of the pylorus and the lesser curvature.

Several macroscopic varieties may be distinguished. The commonest is the annular pyloric carcinoma (Fig. 133), which

forms a dense mass around the distal opening. It extends for a variable distance towards the cardia, becoming gradually thinner till it seems to blend with the normal mucosa. Its surface is ulcerated.

The polypoid, or "cauliflower" type (Fig. 132) forms a large soft tumour which projects into the lumen. Sometimes there

Fig. 133.—Scirrhous carcinoma of the stomach ("leather-bottle stomach"); a rod is passed through the pylorus.

is a diffuse and generalised infiltration of the whole of the viscus with an intensely scirrhous growth. In these cases the wall is dense and rigid and the lumen is contracted, and the condition is known as the "leather-bottle stomach" (Fig. 133). By some authorities the "leather-bottle stomach" is believed to be due to an endothelioma, not a carcinoma, while others regard it as being the result of a chronic inflammatory change. The scirrhous, acellular nature of the growth makes the diagnosis a matter of

considerable difficulty. In another form, the colloid carcinoma, the tumour exhibits an advanced mucoid degeneration. As a rule, this form of cancer tends to crop out on the serous surface and spread widely throughout the peritoneal cavity.

Sometimes a very malignant growth may progress so rapidly through the coats of the stomach wall as to give rise to perforation. *Histologically* the tumours present all degrees between the malignant adenoma, or adenocarcinoma and the carcinoma simplex.

In cancer of the stomach extension is by local spread, and by the lymphatic and vascular channels. The glands chiefly involved are those in the lesser curvature and the pyloric portion of the greater curvature, and the group at the cardiac orifice. Frequently the left supraclavicular glands are also affected. There may often be metastases in the liver and the glands in the portal fissure. Extension of the growth to the outer surface of the stomach is followed by direct invasion of the neighbouring viscera, especially the pancreas, and general dissemination throughout the peritoneal cavity. The ovaries are said to be infected very early in this stage by "droppings" of detached groups of cancer cells. Very occasionally groups of cells may become detached from the inner surface of the growth and transplanted on to the mucous membrane of some part of the small or large intestine. It is particularly noteworthy that direct extension to the duodenum never takes place; the growth always stops short at the pylorus.

Endotheliomata.—Tumours having the features of endotheliomata occasionally occur. Some pathologists regard the scirrhous tumours, usually classed among the carcinomata, as being of endotheliomatous origin.

Secondary Tumours of the stomach are rare; I have found them in 2.23 per cent. of all autopsies on cases of malignant disease. They are usually direct extensions from neighbouring growths.

THE INTESTINES

Innocent Tumours of the intestines are not particularly common. In the connective-tissue group the most usual forms are the ***fibromata, lipomata, myomata,*** and ***angeiomata,*** together with the compound ***fibrolipomata*** and ***fibromyomata.*** They may be situated in the substance of the wall, or

they may project from either surface, being attached by a narrow stalk. The submucous polyp is liable to give rise to ulceration of the adjacent mucous membrane and to a varying amount of mechanical interference with the function of the bowel (Fig. 134). ***Adenomata*** are somewhat rare except in the large intestine, in the lower part of which sessile or pedunculated papillomata of a

Fig. 134.—Intestine opened to show a polypoid fibrolipoma. There is ulceration of the mucous membrane above and below the tumour.

moderate size occur. They may be multiple, and there seems no doubt that at times they become malignant (Figs. 135-136). In the duodenum a papilloma in the region of the papilla of Vater is sometimes encountered, and in the duodenum and jejunum occur small solid adenomata derived from aberrant nodules of pancreatic tissue. In any part of the intestine, but particularly in the large bowel, polypoid tumours due to some chronic irritative change are not uncommon. They are, of course, blastomatoid in nature, and may be seen in enormous numbers in the condition known as colitis polyposa.

Malignant Tumours.—***Sarcomata.***—The lymphosarcoma is a not infrequent neoplasm, occurring chiefly in the ileum,

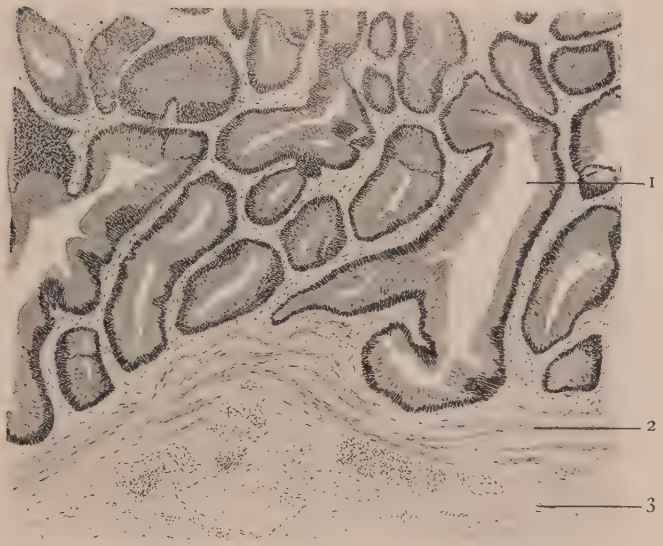

FIG. 135.—Microscopic section through the stalk of a papilloma of the rectum showing (1) gland tubules; (2) muscularis mucosæ; (3) connective tissue of the stalk.
Obj. 16 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

FIG. 136.—Section through another part of the stalk of the same rectal papilloma illustrated in Fig. 135, showing early malignant change. The tubules are now extremely irregular, and the structure is that of an adenocarcinoma.
Obj. 16 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

the cæcum, and the ascending colon (Fig. 137). Other malignant connective-tissue tumours are rare, though the round-, spindle-, and polymorphic-celled sarcomata, and the leiomyosarcoma may be encountered. The lower part of the small intestine and the upper part of the large are the sites usually affected; the

Fig. 137.—Lymphosarcoma of the small intestine forming the apex of an intussusception.

jejunum is less often attacked, while less than a dozen cases of sarcoma of the rectum are on record.

Melanomata are sometimes found in the lower part of the rectum.

Endotheliomata are extremely rare.

Carcinoma.—A considerable proportion, about 10 per cent., of all cancers occur in the intestines, and the great majority of these are large bowel tumours. Though commoner than the sarcoma, the carcinoma is still a rare growth in the small intestine; about half the cases occur in the duodenum, and I have seen at least one example of malignant growth developing in a chronic

peptic ulcer. In the neighbourhood of the papilla of Vater a polypoid adenocarcinoma may be met with (Fig. 138), but most

Fig. 138.—An adenocarcinoma of the ampulla of Vater showing obstructive dilatation of the common bile-duct and metastases in the liver.

of the small intestine tumours are of the scirrhous, adenocarcinoma, or carcinoma simplex, type (Fig. 139). They form very hard annular tumours, and give rise to extreme contraction

of the lumen. Carcinoma may occur anywhere in the large bowel, but is commonest in certain situations; more than half the tumours are in the rectum, while other favourite sites are the cæcum and the first part of the ascending colon, the hepatic and splenic flexures, and the sigmoid loop. In the rectum the tumour is often oval in shape, and occupies one-third or more of the circumference of the bowel; the surface is ulcerated and

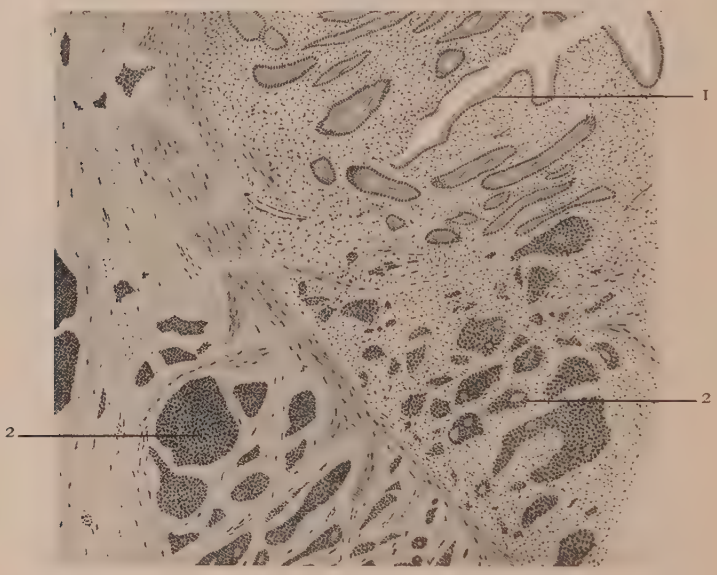

Fig. 139.—Microscopic section from the margin of an adenocarcinoma of the small intestine. (1) Normal mucous membrane; (2) carcinomatous alveoli infiltrating the mucous membrane, and the submucous coat beneath the muscularis mucosæ; acinous formation occurs only occasionally.

Obj. 16 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

depressed, the margins are raised and rolled. Another common variety is the annular constricting type (Fig. 140), and this is the form most often seen in the upper part of the bowel. The polypoid tumour is somewhat rarer. Multiple tumours in any organ are very rare, but in my experience are commoner in the large bowel than in any other organ with the possible exception of the breast. I have seen at least three examples in the colon or rectum where multiple polyps, papillomata, and carcinomata co-existed (Fig. 141).

The paths of extension of a carcinoma of the rectum are of

great importance. It has been stated that permeation along the submucous lymphatic channels, with consequent infection of bowel for some distance above and below the growth, is the rule, and the necessity for the removal of a considerable length of apparently healthy gut has been insisted upon. This contention, however, has not been established, and the more usual

Fig. 140.—Annular carcinoma of the colon causing stricture. There is hypertrophy of the muscle coat above the growth.

mode of extension would appear to be as follows. The cancer cells extend round the bowel in the lymphatic channels of the submucous and muscular coats until the main trunks which pass to the mesentery are reached; permeation then proceeds along these, and eventually there may be a considerable invasion of the glands draining the area involved. Invasion of the blood vessels of the mesentery takes place at an early stage, and emboli are carried to the liver by way of the portal system. In carcinomata of the lower part of the rectum the vascular

metastases are found in the lungs rather than in the liver. I have recently seen a remarkable case in which the lungs were so closely studded with minute metastases that the naked eye appearance was indistinguishable from miliary tuberculosis.

FIG. 141.—A rectum showing numerous polypi (1), villous papillomata (2), and two carcinomata (3).

Vermiform Appendix. Tumours of the appendix are rare; they present no special features, and do not require a separate description. There is, however, one tumour which must be mentioned since it is not very uncommon, and is distinctly anomalous in its characters. It appears usually in the form of a small nodule of a yellowish colour, situated beneath the mucous

membrane. It occasionally infiltrates the wall, reaching to the peritoneal surface, but it rarely, if ever, forms metastases. *Microscopically*, it is composed of solid alveoli of spheroidal cells, lying in a varying amount of fibrous stroma. The general structure is not unlike that seen in certain scirrhous carcinomata of the small intestine, but the tumour cells show no evidence of active growth, and the stroma is quite quiescent. Some authorities regard the condition as being a chronic inflammatory hyperplasia of the lymphoid tissue of the submucosa ; others believe it to be true blastoma, though opinions are still divided as to whether it should be called a carcinoma or an endothelioma. Whatever its nature may be, it cannot be said to have much clinical importance.

Secondary Tumours of the intestine are rare. The bowel may be involved in the local spread of an adjacent growth, and transplantation occasionally takes place on to the mucous membrane of detached fragments from tumours higher up on the alimentary tract.

THE LIVER

Primary tumours of the liver are much less common than secondary metastatic growths, but several varieties, both innocent and malignant, may occur.

Innocent Tumours.—The commonest tumour of any kind is the ***angeioma***. This is usually of the cavernous type, and though included by custom among the blastomata, is probably a blastomatoid formation, arising by dilatation of existing capillaries and secondary hypertrophy of their walls (p. 170). The tumours are frequently multiple, and are more common in old people than in young : they may grow to a considerable size. ***Fibromata, lipomata,*** and ***myxomata*** have been described, but are extremely uncommon.

The ***adenoma*** is also rare. There are two types, one growing from liver cells, the other from the lining cells of the biliary capillaries ; the former is the more common. The ***liver-cell adenoma*** forms a lobulated, nodular growth having a whitish colour ; it is firmer than the surrounding parenchyma, and its limits are clearly defined. It is composed of cells closely resembling those of the normal organ, but having no regularity of arrangement, and exhibiting a good deal of variation of size and shape ; they may be multinucleated, and they often

contain bile. It is difficult to distinguish histologically between the compensatory hyperplasias which accompany cirrhosis, and the liver adenomata, and there is no doubt that most if not all of the examples of multiple adenomata which may be encountered are instances of a reactive hyperplasia. The ***bile-duct adenoma***

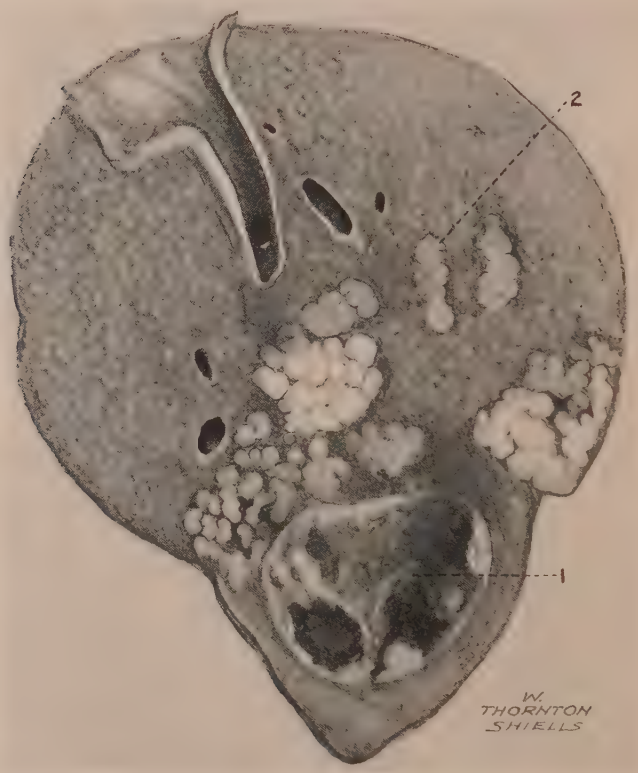

FIG. 142.—Carcinoma of the liver. The primary tumour (1) is hæmorrhagic and bile-stained. The secondary nodules (2) have a lobulated structure and closely resemble areas of regenerated liver tissue.

is a firm, rounded tumour which is often cystic. It is composed of tubules lined by columnar epithelium and supported by a fibrous stroma.

Malignant Tumours of the liver are comparatively rare: carcinomata are more common than sarcomata.

Sarcomata occur as large nodular tumours, or as diffuse growths; they are usually of a pinkish-white colour and a soft

consistence. They are of the round-, polymorphic-, or spindle celled type, and are very liable to hæmorrhages and degenerative changes.

Primary ***melanomata*** have been described, but these tumours are probably always secondary.

Carcinomata may grow from the liver cells, or from the intrahepatic bile-ducts. Several forms of the ***liver-cell carcinoma*** are described. Most commonly there is a massive

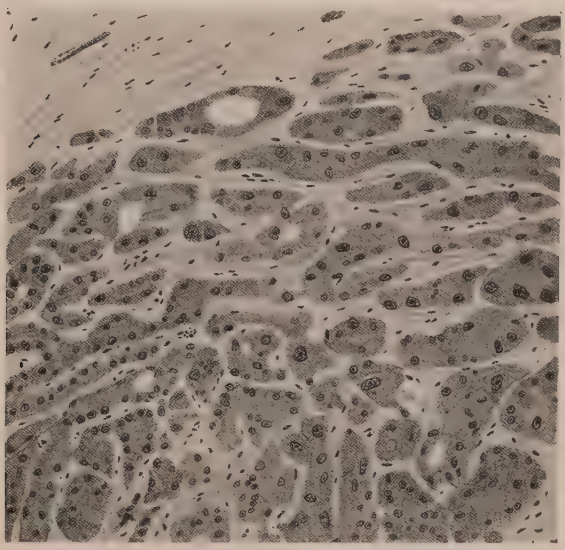

FIG. 143.—Microscopic section of a primary liver-cell carcinoma. In their form and arrangement the tumour cells closely resemble the normal liver cells.
Obj. 8 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

primary growth with several smaller secondary nodules scattered throughout the organ. The small nodules have frequently a very characteristic lobulated structure, recalling the appearance seen in a coarse cirrhosis. The primary tumour is often encapsuled; it is frequently hæmorrhagic in places, and both it and the secondary tumours may be coloured green from the presence of bile (Fig. 142). Sometimes it may not be possible to distinguish the primary growth, for the whole liver contains numerous small tumours. Very rarely the growth takes the form of a diffuse malignant infiltration which gradually replaces the normal cells of the lobules. In some cases cirrhosis appears to

be a predisposing factor, and a special group of tumours are recognised as being associated with this condition.

The *microscopical features* are characteristic. The cells of the tumour are very like those of the normal liver (Fig. 143), though sometimes their protoplasm is clear and vacuolated. Variations in size and shape are common, and small giant cells

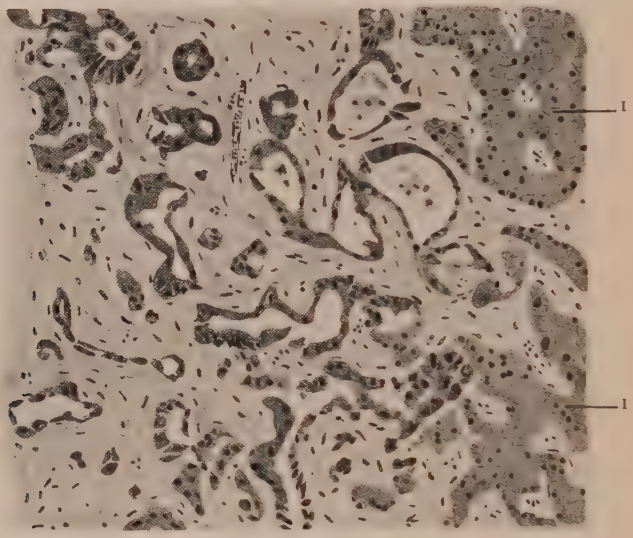

Fig. 144.—Microscopic section of a bile-duct carcinoma of the liver. The tumour consists of irregular acini lined by cubical or low columnar cells, the structure being that of an adenocarcinoma. There is an abundant fibrous stroma. Groups of liver cells can be seen at the right-hand side of the figure (1).

Obj. 8 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

may be formed. The cells may be arranged in columns or as tubules, and are often grouped around deposits of bile. There may be a fair amount of stroma around the larger lobules, but the cell groups are only supported by a small amount of connective tissue.

The ***bile-duct carcinoma*** has no peculiar features, but is like any other adenocarcinoma. There is usually a massive primary growth with secondary tumours in the neighbourhood. *Microscopically,* the tumour is an adenocarcinoma consisting of irregular acini lined by columnar or cubical cells ; there is a variable amount of fibrous stroma (Fig. 144).

Endotheliomata.—These tumours are very uncommon and require no special description,

Adrenal-rest Carcinoma.—This tumour is extremely rare, though some four or five examples have been recorded. Its importance in connection with the origin of the "hypernephromata" in general has already been discussed (p. 189). It must be remembered that there may be a very close resemblance between the cells of a liver-cell carcinoma and the clear vacuolated elements we associate with a hypernephroma.

Secondary growths in the liver are very common in malignant disease; I have found them in 25.28 per cent. of cases in a series of 269 consecutive autopsies on cancerous patients. Certain tumours form metastases in the liver with much greater frequency than others. Thus, my records show hepatic metastases in 22.72 per cent. of cases of cancer of the stomach, and in 28.57 per cent. of cases of cancer of the large intestine, including the rectum. These figures correspond fairly well with the average dissemination in all forms of malignant growth, but in carcinoma of the breast I find that the percentage rises to 52.17 per cent. This considerable increase is largely due to the fact that the mamma is not an organ of vital importance to the individual, and, therefore, derangement of its function by disease is not of immediate consequence; another factor to be reckoned with is the ease with which cancer cells may extend from the breast to the liver by lymphatic permeation.

THE GALL BLADDER AND BILE DUCTS

Innocent Tumours.—Innocent connective-tissue tumours are rare.

Fibromata, lipomata, and ***myxomata*** have been known to occur.

Papillomata and ***cystadenomata*** are somewhat more common, especially in the region of the ampulla of Vater.

Malignant Tumours.—***Sarcomata*** are extremely rare.

Carcinoma is not uncommon. It occurs in the gall bladder, at the junction of the hepatic ducts, and in the ampulla of Vater. A large proportion of the cases are associated with the presence of gallstones. The tumour is usually an adenocarcinoma; in the ampulla it has often a villous or papillomatous structure.

A well-recognised form of growth in the gall bladder is the squamous carcinoma, and I have also met with it in the common bile duct; it is generally regarded as an instance of metaplasia.

Carcinomata of the gall bladder tend to invade the liver at an early stage.

THE PANCREAS

Innocent Tumours.—These are rare and seldom give rise to any symptoms. ***Adenomata*** and ***fibro-adenomata*** may occur as small nodular tumours. One form of pancreatic cyst is a true blastoma, being a ***papillary*** or ***multilocular cyst-adenoma.*** An adenoma derived from the islets of Langerhans has been described.

Malignant Tumours.—***Sarcomata*** are very rare; they are usually of the round-celled type.

Carcinoma.—In my own experience this form of growth is distinctly rare. A clinical diagnosis of carcinoma of the head of the pancreas is not uncommon, but I have seldom been able to verify it post-mortem. The growth may be a carcinoma simplex, but is more usually an adenocarcinoma; it is liable to undergo mucoid degeneration.

THE NERVOUS SYSTEM

THE MENINGES

Innocent Tumours.—***Fibromata*** and ***lipomata*** are somewhat rare tumours which may spring from any part of the dura mater or the pia-arachnoid.

Osteomata occur as flat plaques in the falx cerebri and the tentorium, and also in the spinal dura mater. They are probably not blastomata, but are instances of metaplastic ossification.

Chondromata occur as small soft tumours attached to the membranes at the base of the brain.

Psammomata may grow from the cerebral and spinal membranes, and from the choroid plexus; they are commonest at the base of the brain.

Other very rare benign tumours are ***cholesteatomata, myxomata***, and ***dermoid cysts.*** A ***cavernous angeioma*** is sometimes encountered in connection with the spinal membranes.

Malignant Tumours.—***Endotheliomata*** are the most important malignant tumours growing from the membranes. These have been treated of in a previous chapter (p. 178), and

little more need be said here. They spring from the lining cells of the dura- or pia-arachnoid, or possibly from the capillary endothelium, and form nodular tumours or flat plaques of growth. They are often comparatively innocent, but they may behave as highly malignant tumours, infiltrating the brain and even the skull bones. They are very liable to undergo degenerative changes.

Sarcomata.—These are usually of the spindle-celled type. Other forms more rarely seen are the round- and polymorphic-celled tumours, and the angeio and myxosarcomata.

BRAIN AND SPINAL CORD

Innocent Tumours.—The only innocent tumour of the brain and spinal cord which occurs with any frequency is the ***glioma. Fibromata, lipomata, neuromata, osteomata, angeiomata,*** and ***dermoid cysts*** are described, but are all extremely rare.

Gliomata (p. 101).—These tumours have usually a slow rate of growth, and are very liable to undergo degenerative changes. They vary much in appearance. Sometimes their margins are well defined, and in colour and consistence they are distinctly marked out from the surrounding tissue; in other cases they merge imperceptibly into the normal substance of the brain or spinal cord, and it becomes a question whether they should not be regarded as blastomatoid processes rather than as neoplasms. The fact that there is so often a history of injury some time before the onset of the symptoms referable to the growth of the tumours rather lends support to the view that many of them are blastomatoid in nature.

Malignant Tumours.—***Endotheliomata.***—Primary endotheliomata of the central nervous system are not very common, though the frequency with which they are diagnosed depends very largely on the individual attitude of different observers with regard to these tumours. They can only be distinguished by microscopical examination, and are usually of a more epithelial type than the corresponding tumours of the meninges.

Sarcomata occur as round-, mixed-, or spindle-celled growths. They readily undergo degenerative changes. Although they are usually innocent, gliomata may exhibit malignant properties, growing as gliosarcomata.

Secondary Tumours.—The brain and spinal cord may be invaded by sarcomata and endotheliomata originating in the

membranes or the bones of the skull and the vertebral column, and these tumours may also form metastatic deposits. Metastatic carcinoma is occasionally seen in the brain, especially in the case of mammary and pulmonary cancer.

THE PERIPHERAL NERVES

Innocent Tumours.—Tumours of the peripheral nerves are not common, and it is very rare to encounter a ***neuroma*** or true tumour of nerve cells.

Fibromata occur as nodular tumours growing from the fibrous tissue constituents of the nerve sheath. Blastomatoid fibrous tissue growths of nerves have been described in the section dealing with fibromata (p. 77). ***Myxomata*** and ***lipomata*** are very rare tumours of nerves. ***Neuromata*** are also extremely uncommon, but may be seen in connection with the sympathetic system.

Malignant Tumours.—***Sarcomata,*** usually of the spindle-celled or fibrosarcomatous variety, may grow from nerve sheaths; they do not differ in any way from sarcomata in other situations.

THE EYE

With two notable exceptions, the tumours of the eye are not of any particular interest to the general pathologist. ***Fibromata, lipomata,*** and ***papillomata*** sometimes grow from the conjunctiva, and ***squamous-celled carcinomata*** and ***spindle-*** and ***round-celled sarcomata*** may also be met with in this situation.

The ***gliosarcoma*** originates in the retina; it is a soft hæmorrhagic tumour, and is highly malignant. Superficially, it has the characters of a round-celled sarcoma, but on close examination the cytoplasm of its cells is seen to be prolonged into delicate fibrils which form an interlacing network. The modern view is to regard these tumours as being neuroblastomata, but an absolute diagnosis can only be made when it is possible to apply methods of differential staining.

Melanotic sarcomata are derived from the pigmented cells of the choroid coat. They project into the posterior chamber as rounded tumours of a dense black colour, and have a distinctly sarcomatous histology. They disseminate widely, and are especially likely to form secondary deposits in the liver.

THE URINARY SYSTEM

THE KIDNEY

Innocent Tumours.—The innocent connective-tissue tumours are usually small, though they are often multiple, and although they are not uncommon, they are seldom of any clinical importance.

Fibromata occur in the pyramids, where they form small round tumours, often enclosing one or two tubules in their substance; very occasionally they are found under the capsule. A few examples of fibromata so large as to give rise to symptoms have been recorded. ***Lipomata*** are usually found under the capsule or in the substance of the cortex; they are often combined with a varying amount of fibrous tissue. They are nearly always quite small, but they may reach a considerable size. ***Leiomyomata,*** or, more commonly, ***fibroleiomyomata,*** occur as small tumours growing from the capsule. ***Angeiomata*** have been described as growing to some size in the cortex of the kidney. As a rule they are very small and are really capillary telangiectases; they are situated at the apices of the pyramids, and may give rise to very severe hæmorrhage. ***Myxomata, chondromata,*** and ***osteomata*** have been mentioned as occurring in the kidney, but they are so excessively rare that they may be disregarded.

The innocent epithelial neoplasms form an interesting study from the light they throw on the more important malignant tumours. Small white or yellowish tumours are quite common on the surface of the kidney, especially in the contracted granular organs. Some of them are ***adrenal rests,*** but the greater number are derived from the renal tubules. The majority are quite insignificant, but large adenomata may occasionally be encountered. Three types may be distinguished: (*a*) the ***simple tubular adenoma,*** (*b*) the ***papillary cystadenoma,*** and (*c*) the ***solid alveolar adenoma.*** The last-named forms a rather larger tumour, and is of a darker colour; it is composed of small spheroidal cells lying in a somewhat loose fibrous stroma.

A ***villous papilloma*** may grow from the pelvis of the kidney, and is frequently the cause of serious hæmorrhage.

Malignant Tumours.—***Sarcomata.***—The pure sarcoma is not a common tumour in the kidney, though it may occur at any age. It is usually of the round- or spindle-celled variety.

Endotheliomata.—These are rare. The ***angeiosarcoma*** is in reality an endothelioma.

Hypernephroma.—This is by far the commonest tumour of the adult kidney. It has been treated of in a previous section (p. 182).

Teratoid Tumours.—The mixed sarcoma of infancy appears, as its name inplies, in early childhood. It has been described in the section on teratomata (p. 199).

Carcinomata may grow from the renal tubules or from the epithelium lining the pelvis. The ***renal carcinomata*** occur as nodular tumours or as diffuse infiltrative growths. According to the amount of stroma they contain, they are dense and firm or soft and friable. They grow with some rapidity, disseminating by the blood stream, and also forming metastases in the aortic lymphatic glands. They are adenocarcinomata, and though the glandular structure is often very imperfect, they may sometimes very closely resemble the adenomata. A malignant papillary cystadenoma is a not unusual form. **The *pelvic tumours*** are transitional-celled carcinomata ; very occasionally they may be of the squamous-celled type, exhibiting prickle cells and keratinisation. A malignant papilloma may occur. The pelvic carcinomata very often develop as a late result of the chronic irritation of calculi.

Secondary tumours of the kidney are not common except as a late phenomenon. The infection may reach the organ by direct extension, by the peri-ureteric lymphatics, or by the blood stream.

THE URETERS

A few very rare tumours of the ureter have been described, such as a primary ***transitional-celled carcinoma,*** and an ***adenoma,*** presumably derived from Wolffian remnants. The only neoplasm of any importance is the ***villous papilloma,*** which may grow at the upper or the lower extremity of the tube, projecting either into the pelvis of the kidney or into the bladder.

THE BLADDER

Innocent Tumours.—***Fibromata, myomata,*** and ***fibro-myomata*** are all rare tumours; they tend to become pedunculated. ***Myxomata*** have been described, but are probably merely fibromata which have undergone mucoid degeneration. ***Adenomata*** arising from mucous glands may very occasionally be encountered at the base of the organ.

Fig. 145.—Urinary bladder opened to show numerous villous papillomata springing from the mucous membrane.

The commonest tumour of all is the ***villous papilloma.*** This tumour is frequently multiple, and is much more often seen in men than women. It forms a soft friable growth of a pinkish colour, and consists of a collection of delicate villous processes attached to the mucous membrane by a connective-tissue stalk (Fig. 145). When the tumour is floated out in water, the appearance is not unlike that of a certain type of seaweed. *Microscopically,* the growth is composed of delicate connective-tissue stalks, each containing a central blood vessel and being covered by a stratified epithelium (Fig. 47).

Although the tumour is usually innocent, it must always be regarded with suspicion for the following reasons: it spreads widely by direct transplantation over the surface of the viscus; it tends to recur after removal, since minute outlying tumours may easily be overlooked; and it is often extremely difficult

to determine its nature from a histological examination, for an apparently innocent growth may infiltrate its stalk and invade the bladder wall.

Malignant Tumours.—***Sarcomata*** of the bladder form sessile, fleshy tumours which may be multiple; they are rare, but may occur at any age. An interesting tumour which may be encountered is the rhabdomyosarcoma.

Carcinoma.—Several varieties of carcinoma of the bladder may be recognised. The malignant papilloma forms a friable, cauliflower-like tumour which projects into the cavity of the viscus; at the same time there is a diffuse infiltration of the bladder wall, the tumour having the structure of a transitional-celled carcinoma, or a carcinoma simplex. Sometimes the tumour forms a slightly raised plaque of growth, and this type may be distinctly scirrhous, possessing a large amount of fibrous stroma. An interesting variety is that associated with the presence of the bilharzia ova. In response to the irritation of the ova, the epithelium undergoes a dense nodular hypertrophy, and a squamous carcinoma may eventually develop.

Secondary Growths.—The bladder frequently becomes involved in malignant growths of the rectum and the prostate in the male, and of the uterus in the female. In general peritoneal dissemination secondary tumours may be situated on the fundus.

THE URETHRA

Tumours of the urethra are rare. Small fibrous polypi and ***epithelial papillomata*** are sometimes seen, chiefly in the anterior urethra. A polypoid ***fibro-adenoma*** occurs in the prostatic urethra. The ***urethral caruncle*** of women may be an angeioma, but is much more commonly an area of simple vascular granulation tissue.

Primary carcinoma is quite rare.

THE MALE GENITAL ORGANS

THE PENIS

Innocent Tumours.—***Papilliomata*** occur with some frequency on the glans and prepuce. They form cauliflower-like excrescenses, which may reach a considerable size. The majority of them are to be regarded as irritative hyperplasias, due to the retained secretion under a tight foreskin, or to a venereal discharge.

Very rare innocent connective-tissue tumours are the ***fibromata, lipomata,*** and ***neuromata.*** ***Angeiomata*** have been found in the corpora cavernosa.

Malignant Tumours.—The commonest tumour is the ***squamous-celled carcinoma.*** This usually occurs as a malignant papilloma, but it may form a depressed ulcerated growth with a hard raised border. It appears somewhat late in life, and is frequently associated with phimosis. The majority of the tumours originate at the orifice or on the inner surface of the prepuce, but the glans is often primarily affected, especially in the region of the corona. There is seldom any widespread dissemination, but the inguinal glands are frequently infected.

Sarcomata.—Primary sarcoma of the penis is very rare, but, as in other cutaneous surfaces, ***melanomata*** may occur.

THE PROSTATE

Innocent Tumours.—***Fibromata, myomata. fibromyomata,*** and ***adenomata*** are potential tumours of the prostate, but it is doubtful if they often occur as true blastomata. A very common condition, however, is a diffuse hypertrophy of the organ in which all the elements entering into its composition participate. Simple enlargement of the prostate appears after the fiftieth year; it may be unequal and nodular, or diffuse throughout the gland.

Nothing definite is known of the etiology of the condition, though several theories have been suggested. Some authorities point to the small chronic inflammatory foci which may be demonstrated in the organ as evidence that the enlargement is due to a previous infection; others regard the process as being

a simple senile change, comparable to that seen in the mastitic breast. Though there is overgrowth of both the fibrous and muscular constituents, the most marked change is in the glands. These become elongated and dilated, and their epithelium may show a considerable overgrowth, though the individual cells retain their form. Concretions, known as corpora amylacea, are often present in the tubules (Fig. 146). The adenomatous hypertrophy may be diffuse throughout the gland, or it may be

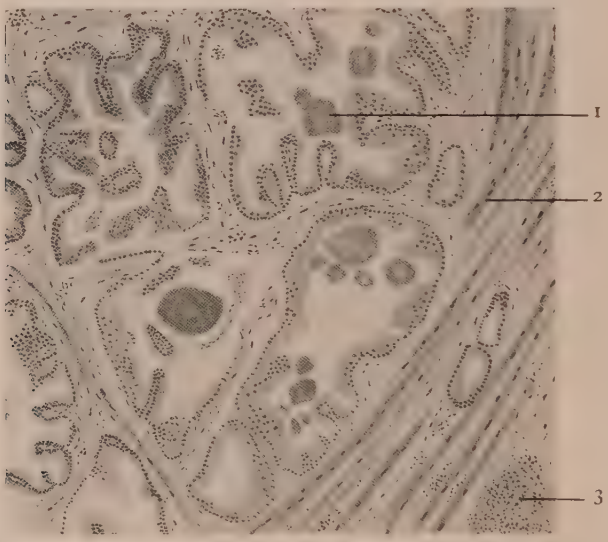

FIG. 146.—Microscopic section of a simple hypertrophy of the prostate. There is glandular hyperplasia, many of the dilated tubules containing corpora amylacea (1); there is also overgrowth of the muscular fibres (2), and small chronic inflammatory foci can be seen in places (3).

Obj. 16 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

peculiarly localised. In the latter condition small nodules, apparently possessing an independent growth, are present in different parts of the organ, and it becomes a question whether we are not dealing with true multiple adenomata rather than with a blastomatoid process.

Malignant Tumours.—***Carcinoma.***—This is probably more frequent than is generally supposed; some statistics show that 10 per cent. of all tumours of the prostate are carcinomatous. The growth is an adenocarcinoma, consisting of small irregular acini lined by low columnar cells (Fig. 147). An encephaloid

carcinoma simplex may also occur. As a rule, growth is somewhat slow, and dissemination is delayed; eventually, however, the bladder becomes invaded, and the aortic glands as high as

Fig. 147.—Microscopic section of an adenocarcinoma of the prostate, showing (1) irregular carcinoma acini, (2) muscle bundles and (3) connective tissue stroma derived from the normal constituents of the gland.
Obj. 8 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

the diaphragm become greatly enlarged with secondary deposits. In some cases numerous metastases form in the bones in all parts of the body.

Sarcomata are rare, but any of the ordinary varieties may be met with.

THE TESTICLE

Tumours of the testicle form a very difficult branch of pathology, and even now there is much confusion in respect to them. This is largely the result of the anatomical peculiarities of the gland, for a neoplasm growing in its substance has to overcome a very serious mechanical obstacle in the stout tunica albuginea. The pressure exercised by this capsule results not only in impairment of nutrition and undue necrosis of the tumour, but also in a partial obliteration of those distinctive histological features

which should help us in arriving at a correct understanding of its nature.

Innocent Tumours.—These are so rare as to be of no consequence. ***Fibromata*** have been described but are probably blastomatoid processes and not true neoplasms. ***Myomata, chondromata,*** and ***osteomata*** must be extraordinarily rare as simple tumours, though muscle, cartilage, and bone may be present in excess in the teratomata. There can be little doubt that the innocent chondroma of the text-books is really a teratoma (p. 83).

Malignant Tumours.—Practically all the tumours of the testicle are actually or potentially malignant. They may occur at almost any age, and are usually unilateral.

Though from the position of the gland one might expect the patients to seek medical advice at an early stage of the disease, the prognosis is not very favourable, for metastases seem to form in many cases before the primary tumour has attained such dimensions as to give rise to anxiety.

Sarcoma.—Many of the tumours which are now classed as alveolar carcinomata were formerly spoken of as sarcomata, so that the incidence of this type of neoplasm is considerably lower than the older text-books would lead one to believe. The sarcomata form soft hæmorrhagic growths, and are often highly necrotic. They are usually of the round-celled variety, but the spindle-celled forms also occur. Metastases are chiefly the result of vascular dissemination, and the old idea that sarcomata of the testicle are especially liable to form secondary growths in lymphatic glands probably arose from confusing these tumours with the alveolar carcinomata.

Carcinoma.—This is generally a carcinoma simplex. Scirrhous forms may be met with, but are rare compared with the more common encephaloid variety. The tumours are composed of polygonal cells, having a clear cytoplasm and bearing a close resemblance to the cells of the seminal tubules. They are grouped together in solid masses separated by a delicate connective-tissue stroma.

Nicholson [1] recognises two types, the alveolar and the non-alveolar, according to the size of the cell masses and the amount of stroma ; in the former, small groups of cells are enclosed in a delicate connective-tissue network, whereas the non-alveolar

[1] *Guy's Hospital Reports*, vol. lxi,

forms are composed of large masses of cells, separated by broad bands of connective tissue.

Endotheliomata.—Tumours derived from vascular or lymphatic endothelium occasionally occur.

Fig. 148.—Teratoma (fibro-cystic disease) of the testicle.

Hypernephroma.—Though this form of growth is not generally recognised in connection with the testicle, it is described by some pathologists. In the section on hypernephromata the occurrence of adrenal rests in the spermatic cord was mentioned (p. 188), and it is supposed that similar rests in the testicle itself may assume neoplastic characters. The clear polygonal cells of the testicular carcinoma are not unlike the cells of certain hypernephromata, but, in the absence of other evidence, this

superficial resemblance is scarcely sufficient to justify such a diagnosis, especially in view of the facts which have been brought forward in recent years in opposition to Grawitz's theory.

Teratomata.—These form a considerable proportion of all testicular growths, but it is unnecessary to add anything more to the description of them which has already been given in the general section on teratomata (p. 197).

Secondary growths of the testicle are very rare, but the gland may become involved in a carcinoma of the scrotum, and I have seen bilateral metastases in a generalised periosteal sarcoma in a child.

THE FEMALE GENITAL ORGANS

THE EXTERNAL GENITALIA

Innocent Tumours.—Fibromata usually grow in the labia majora; they tend to become pedunculated, and may reach a considerable size. ***Myomata, lipomata,*** and ***angeiomata*** are less common.

A ***chondroma*** has been described as occurring in the clitoris.

A rare tumour is an ***adenoma*** of Bartholin's glands.

Warty and papillomatous growths, blastomatoid in nature, are fairly common as a result of chronic infections of the genital tract.

Malignant Tumours.—***Sarcomata.***—These are not often seen, but the round- or spindle-celled forms may be met with.

Melanomata are also rare, though they are rather more common than the pure sarcomata.

Carcinoma.—This is a not unusual form of tumour and occurs as a nodular or papillary growth. It is of the squamous-celled variety, and ulcerates fairly readily. Metastases are found in the inguinal glands. An adenocarcinoma is also described as growing from Bartholin's glands.

THE VAGINA

Innocent Tumours.—Simple ***cysts*** are not uncommon; they usually develop from the Wolffian or Gartner's ducts. ***Mucous polyps*** are almost always of inflammatory origin.

Polypoid ***fibromata*** and ***myomata*** may form large tumours, but they are rare, as are also ***lipomata.***

Malignant Tumours.—***Sarcomata.***—These are not common, but the usual forms may be encountered.

Carcinoma.—Primary carcinoma, though rare, may be seen in any part of the vagina, but most of the cases start at the external orifice or in the posterior fornix. It is of the squamous-celled variety, and forms either a papillomatous or a diffuse nodular growth.

Secondary Growths.—The vagina is very often involved in the growth of a carcinoma of the cervix uteri. In chorion-epithelioma deposits sometimes appear in the vagina, and may be the first manifestations of the condition.

THE UTERUS

Innocent Tumours.—Pure ***fibromata*** and ***myomata*** are occasionally encountered, but the commonest tumour of the uterus is the ***fibromyoma;*** indeed this neoplasm forms a large proportion of all the tumours met with in the female. Fibro-myomata, or fibroids, are composed of interlacing bundles of smooth muscle fibres mixed with a varying amount of fibrous tissue, and form spherical or nodular tumours of a very dense consistence. They are practically always multiple, and may be situated in the substance of the muscle wall, when they are known as interstitial fibroids, or under the endometrium or the peritoneum, forming the submucous and subserous fibroids respectively; in the last two situations they tend to become pedunculated. These tumours are subject to various retrograde changes, among which the fibrous, myxomatous, hæmorrhagic, necrobiotic, calcareous, and putrefactive degenerations may be mentioned. Occasionally, in a uterus the seat of multiple fibroids a sarcomatous change may be manifested in one or other of the tumours. A carcinoma is also said to arise in glandular elements which may have become incorporated in the substance of a fibroid. In both these phenomena it is, of course, difficult to exclude the possibility of the malignant growth being primarily quite distinct from the fibroid. An interesting form of tumour which has already been referred to (p. 96) is the adenomyoma.

The ***chorio-angeioma*** or ***placentoma*** is a rare tumour derived from the chorionic villi of the placenta quite early in

its development. It occurs as a lobulated tumour and is usually single, though occasionally more than one are present. It is composed of embryonic connective tissue containing large numbers of blood spaces varying in size from dilated capillaries to cavernous sinuses, and is covered with trophoblast. [1]

Adenomata of the uterus occur as soft polypoid tumours springing from the endometrium. It is difficult to be certain as to the nature of these mucous polyps, whether they should be regarded as true neoplasms or not, but it is probable that many of them are blastomatoid processes.

Malignant Tumours.—***Sarcomata*** are rarer then carcinomata, and occur at an earlier age. Fibro, myo, and polymorphic-celled sarcomata may arise from the body of the uterus, and round-celled sarcomata from the endometrium.

Carcinomata.—Two types of malignant epithelial new growths are seen in the uterus, the carcinoma of the body, and the form arising from the cervix ; the latter is much the more common.

The cervical carcinoma may arise from the surface epithelium or from the cervical glands, and may be of the squamous-celled type or an adenocarcinoma ; a spheroidal-celled type also occurs. It grows in three main forms, the papillary or cauliflower, the ulcerative, and the diffuse nodular. The growth remains localised in the pelvis for some time, though at a late stage metastases may occur in any part of the body. The broad ligaments and the bladder are often invaded quite early ; later, extension takes place to the rectum, while involvement of the ureters gives rise to hydronephrosis and derangement of the renal functions, so that uræmia is often the immediate cause of death.

The local condition in an advanced carcinoma of the cervix is very terrible. Immediately inside the vulva is a foul cavity representing the bladder and the vagina ; the recto-vaginal septum may also be destroyed, while of the body of the uterus only a small portion of the fundus may be left.

Carcinoma of the body of the uterus is an adenocarcinoma, and occurs as a localised papillary growth or as a diffuse infiltration of the whole of the endometrium. It extends for a variable distance through the uterine wall, and may crop out on the peritoneal surface, but it is much less malignant than the squamous-celled cervical growth, and remains localised for a much longer period.

[1] G. J. Strachan, *Journal of Obstetrics and Gynaecology*, 1923, vol. 30, p. 433.

Endotheliomata.—Tumours having the characters of endotheliomata may grow in the body or the neck of the uterus. It is possible that some of the anomalous spheroidal-celled tumours of the cervix are derived from endothelium.

Chorionepithelioma.—This interesting tumour has already been treated of in the general section on the teratomata (p. 200).

THE FALLOPIAN TUBES

Innocent Tumours.—Primary tumours of the Fallopian tubes are very rare. ***Fibromata, myxomata, myomata,*** and subserous ***lipomata*** may be met with, while of the epithelial neoplasms ***papillomata*** and ***adenomata*** may cause a considerable enlargement of the tube.

Malignant Tumours are even more uncommon, but a papillary and a diffuse ***carcinoma*** may both be seen. ***Sarcomata*** have also been described. A ***chorionepithelioma*** associated with an ectopic gestation is a great rarity, but I have seen two cases, both rapidly fatal.

THE OVARIES

Innocent Tumours.—The innocent tumours of the ovary may be divided into two main classes, the solid and the cystic; both forms are frequently bilateral.

The cystic tumours are by far the commoner, and may be derived from a variety of sources. Though it would be more satisfactory to classify them according to their origin from the Graafian follicles, corpora lutea, Wolffian or parovarian remnants, or the germinal epithelium, this is often impossible, and we have to content ourselves with a recognition of morphological differences.

Several varieties of ovarian cysts are described. The simple mucoid cyst may be unilocular or multilocular. Its wall is composed of fibrous tissue and is lined by a layer of flattened columnar or cubical epithelium. The inner surface of the wall is smooth except for the presence of occasional low ridges which mark the positions of former divisions between separate loculi which have coalesced. The cysts are really misnamed, because the glairy fluid they contain is not precipitated by acetic acid, and is, therefore, not a true mucin. In a rare form of cyst the lining epithelium is distinctly ciliated. Small cysts lined by lutein cells and derived from corpora lutea are not uncommon.

Another variety of ovarian cyst is the ***papillary cystadenoma.*** In this form the epithelium lining the cyst wall shows a tendency to proliferation, so that small warty growths are formed which project into the cavity. This proliferation may be so extreme that the whole cyst becomes filled with a soft, semi-gelatinous growth. In some of the more complex tumours, all grades between the simple mucoid cyst and the complete cystadenoma may be represented in the different loculi. At times the cellular proliferation is so abundant that the solid growth bursts through the wall. When this occurs the tumour cells are liable to become seeded all over the peritoneum, and a condition results which is difficult to distinguish from true malignant dissemination. The confusion is still further increased by the fact that an undoubted malignant change may appear in the epithelium of an ordinary cystadenoma. The cells approach the vegetative type, and the peritoneal deposits are definitely infiltrative in their growth.

Solid benign tumours of the ovary are comparatively rare, but ***fibromata*** and ***myomata*** both occur, the former being the commoner. These tumours are usually extremely dense and hard, but they may become softened from myxomatous degeneration, and pseudo-cysts are sometimes formed in this way. Solid ***adenomata*** occur, but are rare.

Teratomata.—The ovary is peculiarly liable to exhibit this class of new growth. In the majority of cases the tumours are cystic and quite innocent, but more solid, malignant forms may occur (p. 195).

Malignant Tumours.—***Sarcomata.***—These are somewhat rare tumours, but are prone to appear early, even in infancy. The ovarian sarcoma tends to grow and disseminate with great rapidity, and may prove fatal within a few months. *Histologically*, the tumours may be round-, spindle-, or oat-celled, and polymorphic-celled forms are sometimes encountered.

Occasionally sarcoma development may be noted in the wall of a cystadenoma ; I have observed one such case.

Endothelioma.—The incidence of endotheliomata in the ovary, as in other organs, varies considerably with the personal bias of the observer ; and until our standards are more clearly defined this confusion will continue to exist. In the ovary, however, tumours possessing characters which suggest their origin from vascular or lymphatic endothelium are not uncommon.

Carcinoma.—Malignant epithelial tumours of the ovary are probably much rarer than is generally supposed, but both solid and cystic forms may occur. The tumours may be of the spheroidal-celled type, or they may closely reproduce the histological structure of the papilliferous cystadenoma. In the cystic forms the contents of the cysts are usually blood-stained, and there is marked nodular infiltration of their walls. The primary tumour is generally much smaller than the innocent cystadenoma, and peritoneal dissemination is early and extensive. Large tumours, which may be solid or cystic, of a yellowish colour and frequently containing areas of hæmorrhage and necrosis have been described as ovarian hypernephromata. Glynn[1] has shown that these tumours are really luteomata.

Secondary Growths.—As Bland-Sutton and others have pointed out, the ovaries are frequently invaded by secondary growths from the breast or any of the abdominal viscera. Probably many of the malignant tumours of the ovary which are regarded as being primary in that organ are really metastatic growths, so that great care must be exercised to eliminate a primary focus elsewhere when dealing with what is apparently an ovarian carcinoma.

THE BREAST

Tumours of the male breast are merely pathological curiosities ; a typical carcinoma simplex may occur, and also some of the innocent tumours such as fibro-adenoma, but for all practical purposes we may confine ourselves to a consideration of the neoplasms found in the female organ.

THE NIPPLE

The nipple itself is sometimes the seat of tumour formation.

Simple ***papillomata***, tending to become pedunculated, are occasionally seen ; ***angeiomata*** are very rare, and so are ***melanomata***.

A ***squamous-celled carcinoma*** may develop on the nipple, sometimes supervening on a chronic inflammatory process.

Paget's Disease of the Nipple.—This is a condition of considerable importance, though most contradictory statements

[1] Glynn, *Journal of Obstetrics and Gynaecology*, Spring 1921.

as to its nature are to be found in the text-books. In a typical example, the nipple and areolar exhibit a chronic eczematous inflammation which may persist for years. The nipple is depressed, and the area has a raw pink surface, sometimes covered with yellowish crusts. The skin is slightly thickened, and the margins of the affected area are sharply defined. *Microscopically* (Fig. 149), the change is seen to consist in a proliferation of the

Fig. 149.—Microscopic section through a nipple, the seat of Paget's disease. (1) Hypertrophied epithelium showing (2) Paget's bodies; (3) sub-epithelial zone of congestion and round-celled infiltration.
Obj. 16 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

epithelium combined with desquamation, and a very dense, round-celled infiltration of the corium together with increased vascularity. The ducts of the breast are usually dilated, and there is some proliferation of their epithelium. Here and there in the surface epithelium the cells may show a swelling and vacuolation of the cytoplasm, resulting in the formation of the "Paget bodies," which were at one time believed to be parasites. Finally, Paget's disease of the nipple is almost invariably associated with a carcinoma simplex in the deeper parts of the breast, and the main interest of the condition lies in the possible relationship between the two processes.

According to the older theory the eczema of the nipple is the primary condition, and the carcinoma develops later as the result of chronic inflammatory changes, or, possibly, a direct infection, spreading down the ducts.

The more modern theory is that the nipple condition is secondary to the carcinoma of the breast, and is due to changes depending on the obstruction of the lymphatic drainage of the part from permeation of the vessels by the cancer cells. Sampson Handley has demonstrated this condition, and I have seen

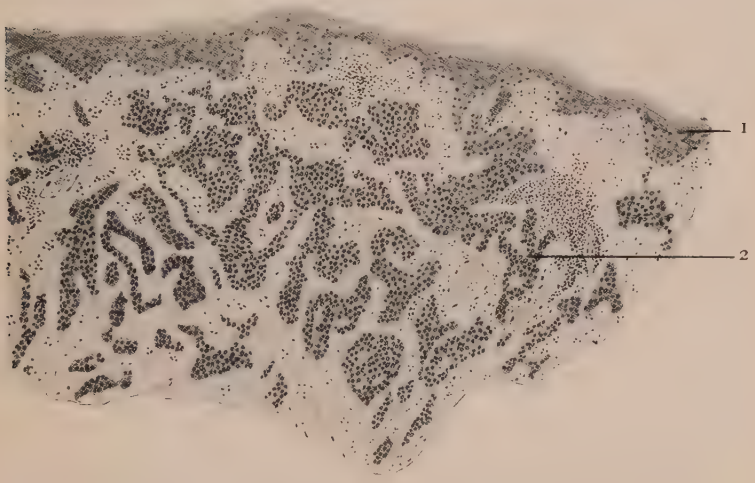

Fig. 150.—Microscopic section through the skin of a breast in the region of the nipple, showing malignant infiltration. (1) Surface epithelium; (2) carcinoma alveoli. Obj. 16 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

several excellent examples of it; there can be no doubt that it is the true explanation in a high proportion of cases.

Two other conditions, closely allied to the true Paget's disease, must be mentioned. In one, a chronic inflammatory condition of the nipple and areolar is followed by the development of a squamous-celled carcinoma, the process being in every way comparable to the development of epitheliomata in other parts of the body in response to forms of chronic irritation. In the other, the eczematous condition of the nipple is secondary to a carcinoma of the breast, but is due to direct invasion of the surface epithelium by the cancer cells, and not to lymphatic obstruction; in other words, the process is simply one of malignant ulceration (Fig. 150).

TUMOURS OF THE BREAST

The breast presents a rich field for the study of tumour-formations, for not only are a great variety of neoplasms encountered in it, but it is also subject to advanced reactive changes of a blastomatoid nature. Our chief difficulty is in distinguishing between true benign blastomata and the very similar blastomatoid formations.

Innocent Tumours.—***Cysts*** of various kinds are quite common. Many of them are of inflammatory origin or due to the obstruction of a duct, but a number occur in the growth of neoplasms and will be referred to under the appropriate headings. Occasionally in retention cysts there are formed small overgrowths of the lining epithelium which project as papillomata into the cavity, and these may sometimes be regarded as true blastomata.

Simple benign tumours of the breast are not common. The pure ***fibroma*** is a rare tumour, though in combination with epithelial elements the fibrous tissue neoplasms are among the most frequently seen of all the mammary new growths. It forms a firm rounded tumour, and often exhibits a considerable degree of myxomatous degeneration.

Myomata, lipomata, and ***angeiomata*** are all rare. ***Myxomata*** have been described, but are probably always degenerated fibromata.

Chondromata and ***osteomata*** are extremely rare.

Papillomata are usually quite small; they grow from the walls of the ducts, and may be multiple. They are composed of branching connective-tissue processes covered by a layer of cubical or columnar epithelium.

Adenomata are not common. They occur, as a rule, as small nodular tumours consisting of tubules resembling the normal breast acini, surrounded by a varying amount of fibrous stroma. They may be recognised microscopically from the fact that the tubules are not arranged in lobules as in the normal gland, and from the absence of ducts.

Another variety is the ***papillary cystadenoma.*** As its name implies, this tumour tends to produce cystic spaces which are filled, partly with a papillary ingrowth of the lining epithelium, and partly with a "colloid" secretion (Fig. 151). In between the cysts are areas of more solid growth consisting of irregular and folded acini. It may be a matter of extreme

difficulty to discriminate microscopically between this tumour and an adenocarcinoma.

The commonest innocent tumour of the breast is the mixed epithelial and connective-tissue growth usually known as the ***fibro-adenoma.*** The name is a bad one since it implies that the adenomatous constituents of the tumour have the greater importance, and this is very rarely the case, for in the majority of tumours it is in the fibrous tissue that the greatest activity is seen, and the changes in the epithelium are secondary.

It would be more correct, therefore, to speak of adeno-fibromata, but the old name is so firmly established that little advantage, and much confusion, would result from any attempt to change.

The fibro-adenoma of the breast forms a firm lobulated tumour which is freely movable under the skin; several may be present in the same breast, and both organs may be affected simultaneously. The majority of the tumours are small, but they may grow to an immense size. *Microscopically*, two varieties are recognised, the pericanalicular and the intracanalicular. In the pericanalicular form there is extreme proliferation of the connective tissue around the acini, so that each tubule becomes surrounded by a ring of fibrous tissue. In this way numerous small lobules are formed, and these are bound together by loose connective tissue, which also shows some hyperplasia. Frequently the periglandular zone shows a well-marked myxomatous degeneration.

FIG. 151.—Papillary cystadenoma of the breast. Some of the cysts contain "colloid" secretion (1), others are filled with a papillary ingrowth of the lining epithelium (2).

As one might expect, this variety of fibro-adenoma is dense and firm, and on section has a peculiarly granular appearance.

In the intracanalicular form the fibrous tissue growth is more diffuse, and the acini become drawn out and distorted. In this way large cystic spaces, lined with epithelium, are produced, and these tend to become filled with a papillomatous ingrowth of the connective tissue (Fig. 152).

Fig. 152.—Fibro-adenoma of the breast showing intra-cystic papillomata (1).

Occasionally this form of fibro-adenoma grows to an enormous size, when it is known as "Brodie's sero-cystic sarcoma" (Fig. 153). It is unusually cellular, and the cysts and their contents are extremely complex. The majority of these tumours are perfectly innocent, but sometimes the connective tissue may assume sarcomatous characters.

Malignant Tumours.—***Sarcomata.***—As compared with the carcinomata, the sarcomata of the breast are distinctly rare. Solid and cystic forms occur, the latter closely resembling the cystic fibro-adenomata, or Brodie's tumours, already referred to. Fibro-sarcomata usually form massive tumours having a comparatively low grade of malignancy. They are very liable to myxomatous degeneration and hæmorrhage, and pseudocysts may be produced in this way. Round-celled and polymorphic or giant-celled sarcomata also occur; they are more malignant than the fibro-sarcomata, and may exhibit a diffuse infiltrative growth.

Endotheliomata.—According to some authorities, who would bring into this group tumours which are described as simple carcinomata by others, endotheliomata are not uncommon in the breast. An angeiosarcoma or perithelioma has been described, and one occasionally meets with diffuse malignant growths composed of small round cells, which appear to be derived from endothelium.

Teratomata.—Mixed tumours having the characters of

teratoblastomata (p. 199) occasionally occur in the breast. They are derived from cells which have become displaced very early in the development of the embryo.

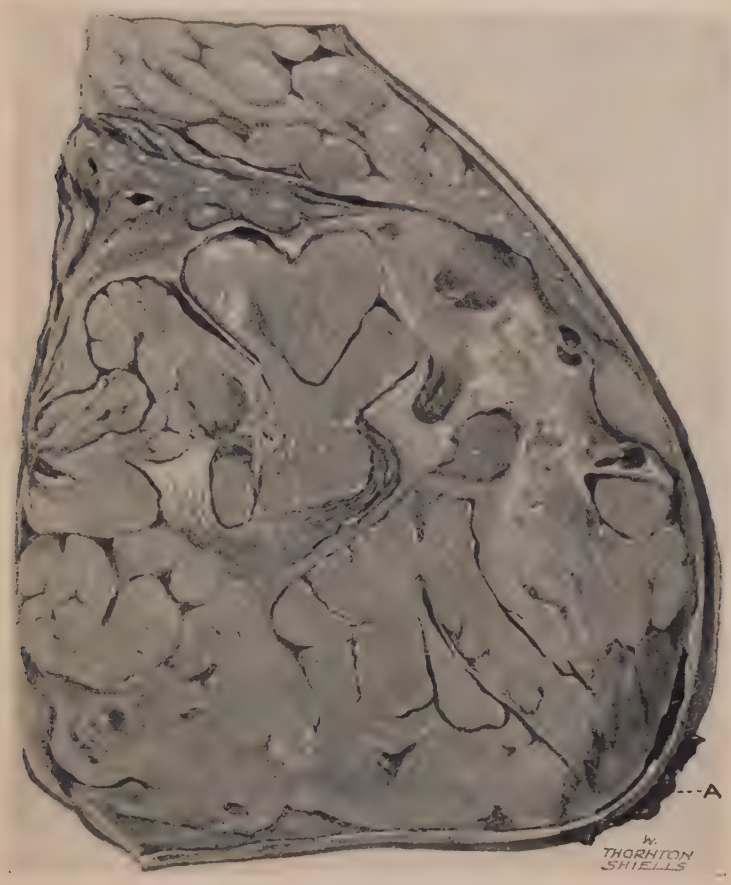

Fig. 153.—Sero-cystic sarcoma, "Brodie's tumour," of the breast. At A the skin has become ulcerated from pressure.

Carcinoma of the breast is extremely common in women between the fortieth and sixtieth years, and nearly one-sixth of the total deaths in females from malignant disease are due to it.

Mammary carcinomata may originate in any part of the gland, though the most common situation is the upper and outer quadrant. The breast may previously have been healthy, but very frequently it shows fairly advanced chronic mastitic changes.

The size and consistence of the tumours are variable, depending on the nature of the growth and the amount and character of the stroma. The commonest type, the scirrhous cancer, forms a small nodular tumour with an irregular outline; it is extremely hard, and on section has a peculiar "woody" appearance, often likened to an unripe pear (Fig. 154). Another variety, the encephaloid carcinoma, forms a rounded, considerably larger tumour of a softer consistence (Fig. 155). Degenerative changes are common in this type, and its cut surface may be studded with small points of necrosis, remarkably like tiny abscesses. Occasionally a tumour may exhibit such marked mucoid degeneration that the term "colloid carcinoma" is applied to it. Another type, the duct carcinoma, is a softish, rounded tumour arising beneath the nipple in relation to one of the lactiferous ducts. Sometimes the growth instead of being circumscribed is diffuse, and may exhibit an irregular formation of cysts. Finally, carcinomata may start in connection with simple cysts, either as nodular growths in their walls, or as intracystic papillomata.

FIG. 154.—Scirrhous carcinoma of the breast, showing retraction of the nipple (1) and secondary deposits in the axillary glands.

Histologically, the growth is usually a carcinoma simplex, either of the scirrhous or the encephaloid type. Adenocarcinomata, generally supposed to arise from the ducts, are also fairly common, and so are intermediate forms between the two. The malignant papilliferous cystadenoma is a much rarer growth.

The growth and dissemination of mammary carcinomata are matters of extreme interest, for on a proper understanding of them depends the possibility of successful operative treatment. As Handley has demonstrated, dissemination takes place chiefly

by a process of lymphatic permeation, which is responsible for most of the cutaneous, lymphatic, intrathoracic, and abdominal metastases. The general nature of the process has already

Fig. 155.—Encephaloid carcinomata of the breast. The nipple (1) is pressed to one side, and the skin is ulcerated (2). There are secondary deposits in the axillary glands (3).

been described (p. 27); for its particular application the reader should consult Handley's original monograph. In no other variety of malignant growth are the metastatic tumours so numerous or so widely spread, and it is interesting to note that carcinomata of the breast share with similar tumours of the

thyroid and the prostate the peculiarity of forming secondary growths in bones more frequently than any other neoplasm.

With the possible exception of the uterus, multiple tumours are more common in the breast than in any other organ.

Innocent fibro-adenomata or simple cystic tumours are frequently seen in association with carcinomata, while multiple benign tumours may show a considerable variation in their structure.

Primary multiple carcinomata have been described, though it is always difficult to establish beyond all possible doubt a separate origin for the different tumours.

A very few cases of the simultaneous growth of carcinoma and sarcoma have been recorded, but in none of them was there any very clear evidence that either tumour had any etiological relationship to the other. One might be prepared for the development of a sarcoma in the stroma of a chronic carcinoma, but this has not yet been demonstrated; indeed, in a case of combined carcinoma and sarcoma which I have recorded,[1] the sarcoma appeared to be the primary tumour.

THE DUCTLESS GLANDS

THE THYROID GLAND

Innocent Tumours.—***Adenoma.***—Localised or general enlargement of the thyroid is a very common condition, and it is a matter of the greatest difficulty to distinguish between simple reactive hyperplasias and true blastomatous formations. There is very little in the histological structure to assist one in arriving at a diagnosis, for the adenomata may closely resemble the normal gland, while the microscopical features of the hyperplastic organ may be highly atypical. Adenomata of the thyroid form rounded encapsuled tumours; they are usually multiple, but are very seldom larger than a tangerine orange. On section they present a very variable picture: they may be of a brownish-red colour and contain numerous cystic spaces filled with colloid; or they may be solid, of a paler colour, and of a distinctly myxomatous appearance; sometimes they are of a yellowish colour and of a much denser consistence. They are, as a rule, highly

[1] *Lancet*, September 14, 1912.

vascular, and often contain areas of hæmorrhage, while central cystic degeneration and foci of calcareous infiltration are common.

Microscopically, the commonest tumour is one whose structure resembles that of the normal gland. It is composed of acini, differing greatly in size, lined by cubical epithelium, and filled with colloid material; small immature acini are frequently present at the periphery of the growth. Blood vessels are

Fig. 156.—Microscopic section of a cystic adenoma of the thyroid, showing irregular acini lined by cubical epithelium and filled with colloid.
Obj. 8 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

numerous and pass in close contact with the epithelium; the stroma is usually scanty, and is often highly œdematous and acellular in appearance (Fig. 156).

In another type, the fœtal adenoma, the structure of the embryonic gland is reproduced. This tumour consists of small empty tubules, lying in a delicate vascular stroma (Fig. 157).

Sometimes the acini of a thyroid adenoma may be unusually large and partly filled by a papillary ingrowth of the lining epithelium, which may become quite columnar in shape, so that a distinct papillary cystadenoma is formed.

Parathyroid adenomata may occur within the substance of the thyroid or in its immediate neighbourhood. They reproduce

the structure of the parathyroid fairly accurately and are usually extremely vascular.

Innocent connective-tissue tumours of the thyroid are practically unknown; ***fibromata, angeiomata, chondromata,*** and ***osteomata*** have been described, but are merely curiosities and of no importance.

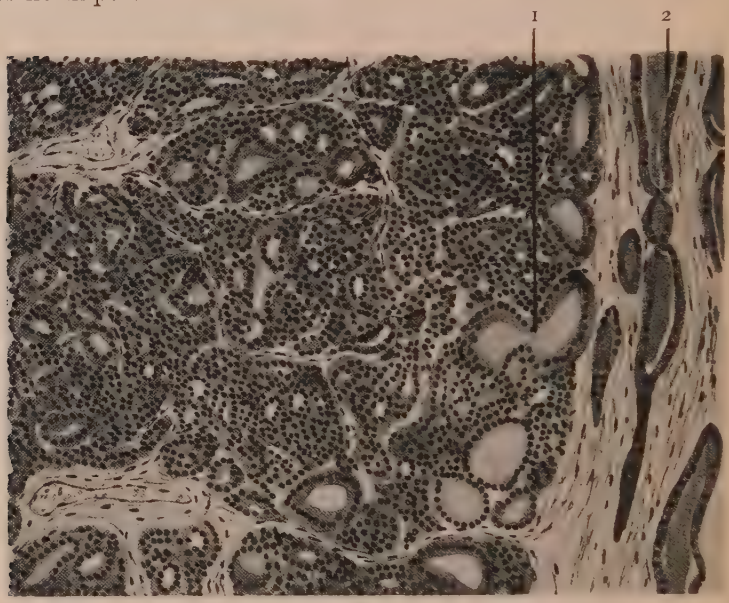

Fig. 157.—Microscopic section of a fœtal adenoma of the thyroid. The structure is that of a tubular adenoma, and though the majority of the tubules are badly formed, some of them are dilated and contain secretion (1) which, however, is not true colloid. At the right-hand side the normal thyroid tissue is compressed to form a capsule (2).

Obj. 16 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

Malignant Tumours.—***Sarcomata*** are rare, but occur as highly malignant growths which spread rapidly to the tissues of the neck. They are usually of the round-, spindle,- or polymorphic-celled type, and highly vascular forms, known as angeiosarcomata or peritheliomata, are also described.

Carcinomata are also rare; they are prone to develop in previously enlarged organs. The thyroid carcinomata have not been studied with so much thoroughness as many other tumours, and very conflicting statements have been made with regard to them. Some forms appear to be extremely malignant, spreading to the tissues of the neck at an early stage, and giving rise

to distant metastases, especially in the bones; other varieties grow much more slowly and show little tendency to dissemination.

The *microscopical* structure of the tumours is equally variable (Fig. 158). In some cases the growth cannot be distinguished histologically from a simple thyroid adenoma, and only by the demonstration of an infiltrative growth or secondary deposits

FIG. 158.—Microscopic section of a carcinoma of the thyroid. The tumour is composed of large masses of cuboidal cells which occasionally form colloid-containing acini (1) supported by a scanty connective stroma.
Obj. 8 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

can a diagnosis be made. In these cases the tumour and its metastases produce colloid, and appear to be capable to some extent of performing the functions of the normal gland. Another variety of tumour contains no colloid, but has the structure of a glandular or simple carcinoma, and in the absence of any of the characteristic features of the thyroid it may be impossible to prove that it originated in the gland, though the naked-eye appearances may strongly suggest such a source.

Instances have been recorded of the occurrence of combined carcinomata and sarcomata of the thyroid; indeed, such mixed tumours are said to be more common here than in any other

organ. It must be remembered, however, that the histology of thyroid tumours, especially the rapidly growing ones, may be most complex. Occasionally the tubular structure may be entirely absent throughout the greater part of the growth, and, as the result of compression, the cells may assume a distinctly sarcomatous appearance. These tumours are often extremely puzzling, and it is only by an examination of several sections taken from different parts that a true conception of their nature can be obtained (p. 159).

It is worthy of notice that many thyroid tumours are exceedingly vascular, so much so that they may actually form pulsating tumours.

THE THYMUS

The only tumour of any importance derived from the thymus is the ***lymphosarcoma,*** one of the forms of mediastinal tumour; this has been described in a previous section (p. 117).

Other forms of sarcomata are occasionally met with.

Dermoid cysts sometimes arise from the Hassall's corpuscles, and ***squamous-celled carcinomata*** may also develop from these epithelial "rests."

THE SUPRARENAL GLAND

Developmentally, the suprarenal gland has a double origin, the medulla being derived from the sympathetic nervous system, while the cortex is formed from the mesodermal cells covering the Wolffian body. We see a corresponding difference in the blastomata of the cortex and the medulla.

Innocent Tumours.—***Adenomata.***—A nodular or adenomatous hypertrophy, in which the suprarenal cortex is studded with little spherical tumours of a yellowish colour, is quite common, and true adenomata are not infrequently seen. They are usually small tumours, and resemble in their structure the zona fasciculata of the normal cortex.

Innocent ***gliomata*** and ***ganglioneuromata*** are rare tumours occurring in the medulla. Other benign neoplasms which have been described are ***lipomata*** and ***angeiomata***.

Malignant Tumours.—Primary malignant tumours of the suprarenal, though somewhat rare, are of very great interest.

Sarcomata may grow from the medulla or the cortex. They

occur chiefly in children, and are usually of the round-celled or lymphosarcomatous variety; they are peculiarly liable to form metastases in the skull bones. Another group of sarcomata are derived from the nervous elements of the medulla. They are usually described as gliosarcomata, but it seems probable that they are really neuroblastomata. They occur in children, and may be bilateral.

Paragangliomata both innocent and malignant are derived from the chromaffin cells of the medulla and are allied to the neuroblastomata.

Melanotic sarcomata have also been recorded.

Carcinomata.—Malignant epithelial tumours of the suprarenal are not particularly common, though they occur both in children and adults. They are derived from the cortex of the gland, and have the structure of hypernephromata, or of atypical spheroidal-celled carcinomata. In children they have a remarkable effect upon the general physiology of the body, being almost invariably associated with precocious development of the reproductive glands and the secondary sexual characters.

THE PITUITARY GLAND

Tumours of the pituitary gland are chiefly of interest from the relation they bear to the condition known as acromegaly, but it must be borne in mind that they may be entirely unaccompanied by acromegallic symptoms.

Innocent Tumours.—The most important benign tumour is the ***adenoma,*** which is often of the cystic variety. As in the case of the thyroid, an adenomatous hyperplasia occurs in the pituitary body and is really more common than true adenomata. Among other innocent tumours, ***angeiomata, lipomata, neuromata,*** and ***teratomata*** may be mentioned.

Malignant Tumours.—Sarcomata and carcinomata both occur, and from their situation give rise to severe symptoms from involvement of the optic chiasma and destruction of the base of the skull.

The ***sarcomata*** are of the round- and spindle-celled variety; the ***carcinomata*** are usually of an atypical squamous-celled type. ***Endotheliomata*** may also occur primarily in the pituitary.

THE CAROTID BODY

From the carotid body is developed a well-recognised tumour, the ***paraganglioma*** or ***"potato tumour."*** It is derived from the specific chromaffine cells of the gland and resembles similar tumours of the adrenal medulla. It forms an irregular oval

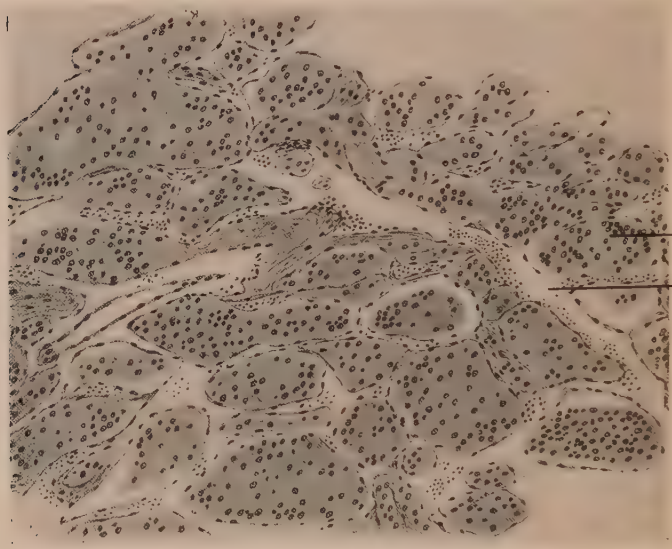

Fig. 159.—Microscopic section of a carotid body tumour. The tumour consists of alveoli of spheroidal cells (1) lying among dilated thin-walled capillaries (2). Obj. 16 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

body of a firm consistence and a yellowish colour. It possesses only a low degree of malignancy, and seems never to form metastases.

Histologically, the tumour is composed of large spheroidal cells, which are grouped together in solid alveoli between a system of widely dilated capillary blood vessels (Fig. 159).

THE COCCYGEAL BODY

Very little is known about the tumours of the coccygeal body, but ***peritheliomata, angeisarcomata,*** and ***chondromata*** have been described as occurring in it.

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